A TREATISE ON TROPICAL THERAPEUTICS

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In Medical and Veterinary Practice
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A TREATISE ON TROPICAL THERAPEUTICS

VOLUME ONE

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PREFACE

The favourable reception accorded to the first edition of this book, which was published in 1936, though gratifying to the author, was offset by the fact that the book remained out of print for several years. In spite of the pressing demand by the post graduate students and by the practising physicians, it has not been possible to bring out a new edition earlier. The constant demand for urgent work, the confusion caused by the World War II and the difficulty in getting paper were some of the factors responsible for this delay.

During the intervening decade considerable progress has been made through systematic research in tropical medicine and therapeutics and quite a large number of drugs of great value has been introduced for the treatment of different tropical diseases. In fact, so rapid has been the progress that physicians find it increasingly difficult to keep pace with it. Moreover, the importance of appreciating the pharmacological action of drugs as the basis for their scientific use is becoming more apparent in the practice of modern medicine than in any other time before. Recognising therefore, the immensity and importance of the rapid growth of Therapeutics and with the objective of making available all the useful information in one book, which can be used both as an advance text book and as a work of reference, the present edition has been largely re written. In fact, almost every page has received attention and several new chapters and sections have been added, so that this edition may be regarded as an entirely new work. In addition to the therapeutic advances, clinical aspects of various disease conditions in which drugs are recommended to be used have been incorporated in this edition in a little more detail with a view to bring home to the physicians the exact methodology of their administration in clinical work. While every effort has been made to keep the text abreast of the modern advances in the subjects discussed it should be realised that the progress has been so rapid, especially with regard to several chemotherapeutic

agents and antibiotic drugs, that a book becomes almost out of date by the time it leaves the press It has, therefore, been decided to include further newer developments at the end of the book as an Addendum

It is a pleasure to acknowledge the help that the senior author has received from Drs B Mukerji and I C Chopra, both his former students and co workers at different periods The contribution and helpful co operation received from them have been of great value In fact, it would not have been possible to bring out this edition without their active help and this is best acknowledged by including their names as joint authors Thanks are also due to Drs S Bhattacharya, S P De, J R Kohl and many others, for active assistance in checking the proofs, etc

The latest findings of science are always based on previous work of innumerable investigators Therefore, it is obviously difficult and sometimes impossible to give full credit in all instances to every one concerned The authors have freely consulted the writings of many of these contributors Our acknowledgements are herewith extended to all of them and full credit has been given to them, whenever possible, in the text

To facilitate early publication of some of the important matters and to meet the growing demand the book is brought out, initially, in two volumes It is intended eventually to combine them into one volume with full Index and references, when the second volume is ready

Criticisms and suggestions for improvement will be gratefully received

R N Chopra
D ug R r h Labora ory Jammu Ka lmr Sa e
B Mukerji
Cen al D ugs Labora ory Ca u a
I C Chopra
D ug Resea h Labo a ry Jammu Ka hm Sa e

June, 1950

PREFACE TO THE FIRST EDITION

Since 1921 I have been engaged in teaching post graduate students at the Calcutta School of Tropical Medicine and nearly a hundred medical practitioners from all parts of India and some from other tropical countries have annually passed through my hands. Medicine is taught in the Medical Schools and Colleges of India chiefly from British and American text books where the climatic and the morbid conditions are somewhat different from those in the tropics. It is not surprising, therefore that the therapeutic methods described therein are not universally applicable in the environment under which the medical practitioners work in the tropics. It is not unusual to meet with disappointment in results and even untoward effect from the applications of such methods.

The importance of this fact has impressed me so greatly that I have thought it worth while to review the whole subject of therapeutics with due regard to the climatic conditions met with in the tropics generally and in India particularly. All the experience gained during the last fifteen years of intimate association with post graduate teaching and treatment of patients in a well equipped research hospital such as the Carmichael Hospital for Tropical Diseases has been collected and put together in book form so that the information is readily available. To encourage the rational use of drugs, the pharmacological actions of various remedies have been described before their therapeutic uses are discussed. The ætiology and pathology of disease have been mentioned briefly only in so far as it is necessary to make the treatment more comprehensible. These additions have made the book somewhat bulky.

I would like to emphasize that not only does this book include the results of my own personal experience but that of many of my colleagues and co workers in the Calcutta School of Tropical Medicine who have very generously helped me in producing this volume. Had

it not been for this co operation and help the task would have been an impossible one Every section of the book has thus been thoroughly scrutinised by various experts on particular subjects, who have liberally contributed valuable criticisms and suggestions, which have been incorporated In this connection I would like to put on record my very great indebtedness, my sense of gratitude and appreciation for the help which has been *ungrudgingly given me by everyone* concerned

* * * * *

The book is so designed that it will not only serve as a reference book for medical practitioners in the tropics but will also meet the requirements of senior students appearing in their final examinations In spite of the great care that has been taken, the book possibly has many shortcomings and blemishes I shall be very grateful for criticisms and suggestions so that in the next edition these defects can be removed

R N CHOPRA

Calcutta
School of Tropical Medicine,
April, 1936

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1. Source and Nature of Drugs

Histo

The problem of cure of disease has faced mankind as far back as memory can take us and he has looked for remedies to alleviate his sufferings from the earliest times The evolution of drugs is traceable to the desire of man to overcome personal discomforts arising from disease In course of time the

vated, they are collected and active preparations are made from them The very name drug comes from the Anglo Saxon word *drugon* meaning to dry Crude drugs are the commercial form of plant drugs as they are brought to the market They yield one or more definite chemical bodies of medicinal value which are known as active principles or active constituents These constituents may occur in the whole plant or in one particular part, *e g*, leaves, roots seeds, etc

Synth

Besides drugs of vegetable origin, there is a large group of drugs known as chemicals Many chemical compounds are produced by plants, by natural processes at ordinary temperature and pressure, *e g*, alkaloids, glucosides, salts etc To produce similar compounds artificially, the chemist has to resort to powerful reagents such as strong acids and alkalis, large variations in temperature and pressure, distillation fusion and many other drastic operations Many of the products of the chemist are similar in action and composition to natural compounds but they are cheaper to produce Other chemicals belonging to the inorganic class are produced from natural minerals, sometimes by simple processes at other times by complicated ones Then there are the comparatively recent remedial agents obtained by various chemical operations, mainly from

coal tar as well as other products obtained by the more or less complicated processes of synthesis There are also the so-called organometallic compounds which form a powerful and important group particularly in the treatment of protozoal diseases *These compounds have to be prepared with extreme care*, as many of them are positively dangerous, unless they are in a state of absolute purity

Biological products, such as vaccines, sera, gland products, hormones, bacteriophages, penicillin and other anti biotics, etc, form another group of *remedial agents* They require even greater skill and more expert knowledge than any other type of preparation used in medicine

2. Action of Drugs as Basis of Therapy

Pharmacology is the term applied to the science which deals with the action of drugs upon anim [illegible] ieir application in disease It, in f[illegible], which forms the basis for their [illegible] the alleviation and prevention of p[illegible] pharmacology deals with the reac[illegible]ronment, these changes being produced by drugs

Therapeutics has been defined as the art and practice of treating abnormal states by any method that relieves pain, restores health or prolongs life It comes from the Greek word *therapeutikos* meaning healing, curative alleviative It includes all remedial agents and measures used in the treatment of disease

In old days treatment was largely symptomatic and the name allopathy was given to it Remedies such as purgatives blood letting, etc, were used to suppress the symptoms of diseases This was followed by the study of drugs upon normal individuals and the experimental science of pharmacology was born

Therapeutics may be empirical or rational The former includes any measure which experience has shown to be beneficial but whose action cannot be explained, rational therapy on the other hand consists in using drugs whose mode of action is understood

The foundation of rational therapeutics was laid in the second half of the nineteenth century with the development of the science of pharmacology and critical study of the action of drugs on the functions of the body It was considerably helped by rapid advances made in organic chemistry and production of powerful chemotherapeutic agents Biochemistry also developed side by side, and *insight into the role of vitamins, endocrines etc* led to *their use in the* treatment of disease During the last three decades the science of therapeutics has been *developing on sound lines, and while great advances have already been* made, more are expected in bringing diseases under control

In the treatment of disease full use should be made of all the measures available In any improvement produced in the condition of the patient by the application of these measures the part played by nature must not be forgotten Nature is infinitely wiser in the art of healing than we imagine Variations from normal in disease are often an effort on the part of nature to meet the needs of the patient and should not always be considered as *harmful* *Proper use of* therapeutic measures renders important help to these forces in curing disease in the least time and with least harm to the organism The task of the physician consists in directing the treatment in such a manner as to remove the obstacles

Guiding principles

which hinder the path of natural cure This should be done by a thorough comprehension of the diseased conditions that is by diagnosing the case as carefully and as fully as possible Before ordering a drug or method of treatment the physician should have a clear conception of what he is trying to accomplish Drugs should not be prescribed unless there is a distinct indication for them The doses of all the remedies should be very carefully considered to fit the needs of the patient's conditi[illegible] influential factors which have an impc[illegible] as the maintenance of the vitality of [illegible] of toxins by the kidneys bowels and [illegible] giving to the patient sufficient physical and mental rest and sleep

Physicians should not rest content with the relief of symptoms alone but should strike at the root cause of the disease Unfortunately for many of the diseases attacking man, specific remedies do not exist The progress of chemotherapy during recent years has however produced a large number of effective remedies against helminthic, protozoal and bacterial diseases In this the commercial manufacturing organizations have played a very important part

Commercial repercussions

Unfortunately effective new compounds are at first patented by one concern but in course of time rival manufacturers evade these patent rights by slightly altering the formulae and giving their modifications new names The natural result is a confusion in the mind of the practitioner who is presented with a host of proprietary labels covering compounds which possess almost the same therapeutic action Extensive advertisement which is a normal feature of modern drug concerns is sometimes lent to remedies which have no proved value This practice makes it incumbent upon the part of medical men to use only those remedies the composition and action of which they have knowledge

3 The Mode of Action of Drugs

Effective concentration

It has been amply proved by modern research that many drugs act in very high dilutions The unit dose of such compounds is expressed in fractions of a gamma (1 mgm=1 000 γg) and some substances produce effects on isolated organs in dilutions of 1 part in 10 000 million As there are 6×10 molecules in a gram molecule of any chemical a solution of adrenalin at a dilution of 1 in 10 000 million contains about 10 000 million molecules in a drop It is therefore not correct to assume that science of chemistry and its laws have no bearing on the science of pharmacology The action of a drug depends on the drug attaining a certain concentration in the blood stream and tissue fluids and a chemical reaction between the drug and the cells Our knowledge of these chemical changes is as yet too limited to show how selective chemical changes are brought about upon a complex system (Applied Pharmacology by A J Clark)

Drugs may act independently outside the body (antiseptics on micro organisms), they may act in or about the body, but not on its structures (sulphur on ringworm of skins) and lastly they may act on the tissues of the body itself On the tissues of the body the drugs may act by physical or chemical means

Physical and Chemical actions

In physical actions no remarkable chemical reaction occurs between the drug and the tissues The examples of physical action are the protective effect of oils dusting powders etc osmotic effects or salt actions of isotonic, hypotonic or hypertonic solutions, adsorptive or absorptive action of carbon dyes infusorial earths and the colloids generally

Some drugs exert chemical reactions within the body which may be of the nature of combination or substitution By combination is meant the direct union

found to stimulate one structure and depress another, e.g., atropine stimulates the vagus centre and depresses the vagus endings, pilocarpine stimulates the nerve endings in sweat glands and depresses heart muscle

f

The intensity of the action of a drug depends on, (a) the concentration in which it reaches the particular cells on which it acts and, (b) the duration for which this concentration is maintained *The concentration which a drug attains* in the body depends on —(1) The rate of its absorption, and (2) the rate of its removal from the body which occurs in two ways —(a) Excretion by kidneys lungs, skin, etc (b) Chemical destruction in the body by processes of oxidation or reduction, or by the formation of inert bodies in combination with such compounds as glycuronic acid, glycocoll and sulphates

7. Absorption and Distribution of Drugs

The local action of drugs occurs irrespective of absorption but for general action, absorption is necessary There may, however, be local general and specific actions from the same substance, e g, phenol In many cases the object of administration is that they may be absorbed into the blood and produce their *specific effects For this purpose a drug may be (1) applied to the skin but* here absorption takes place with difficulty as it has to be taken up through the sweat glands, *the horny epithelium of the skin being impermeable*, (2) when administered by the mouth the drugs are absorbed from the gastro intestinal tract, (3) when injected subcutaneously, intramuscularly intravenously or into one of the serous sacs absorption takes place rapidly

on

When given by the mouth, which is the commonest mode of administration, drugs are absorbed principally by the upper portion of the small intestine, very little absorption occurs from the stomach in case of most of the drugs Experiments have shown that the isolated rectum absorbs certain substances at least as well as the small intestines, owing to its abundant vascularity Strychnine 1½ grain put directly into the stomach of an animal produces con*vulsions in 30 minutes, in the small intestines in 10 minutes, in the œsophagus*
...s From
Alcohol
es absorp
tion of other substances dissolved in it, because its irritating effect improves the circulation Such effects are reversible and the absorption of alcohol may be slowed by non absorbable drugs such as cascara Substances such as oleo resin of male fern are absorbed more quickly
Absorption from both the stomach and inte...
the amount of food present and in some case
with the drug Absorption is more rapid fr...
gastro intestinal tract *Absorption occurs readily from the small and more slowly* from the large intestines Foodstuffs that are not absorbed from the small intestines are often absorbed from the large gut In medical practice rectal feeding has sometimes to be resorted to in persons unable to swallow, predigested foods and glucose are readily taken up Toxins are also absorbed *in the same* way The rate of absorption depends on the method of administration of a drug and occurs in the following order beginning with the most rapid —
... hypoderm... through mucous mem
and from skin
thus in shock
...ut which does
...ay decrease it,

ulceration of the mucous membrane increases the absorbability of many drugs Astringents tend to lessen absorption and saline solutions such as magnesium sulphate and other cathartic drugs which are but little absorbed themselves may prevent the absorption of other drugs and even water

Selective absorption

The r [illegible] allows the ready absorption [illegible] understood Why K or [illegible] obscure The intestinal [illegible] It should also be noted that the presence in the alimentary canal of nonabsorbable substances hinders absorption of others *e g*, absorption of strychnine in the isolated piece of gut is delayed in presence of magnesium sulphate Some gases such as hydrocyanic acid phosgene nitrous oxide and ethylene are absorbed rapidly by the lungs while ammonia is but little absorbed

Solubility

Only soluble substances can be absorbed but it should be remembered that solubility is modified by chemical changes in the alimentary canal, insoluble substances are rendered soluble by the action of juices and are then taken up Solid substances such as carbon iron etc are taken up through the agency of phagocytes and may be found in the mesenteric blood and lymph nodes Such solids exert no action unless dissolved in the body fluids The rate of absorption is modified by the solvent Solutions in alcohol are more rapidly absorbed than water solutions The more soluble a substance is in protoplasm the more quickly it is absorbed The concentration of the solution may vary the rate of absorption The absorption area modifies the rate of absorption *e g* multiple hypodermic injections are absorbed much more quickly than if the same amount of fluid were injected in one place at once

Volatility

Volatility is another factor which influences absorption Hydrocyanic acid is absorbed rapidly and causes instantaneous death when concentrated Most volatile substances if swallowed are rapidly absorbed from the gastro intestinal tract Colloids such as gums and resins oils kaolin (Fuller's earth) charcoal and other inert powders and plant residues when mixed with absorbable materials such as salts and alkaloids lessen the rate of absorption—partly by fixing them selves to the drug and partly by hindering access to the absorbing surface Isolated active substances (alkaloids) are therefore preferred if quick systemic action is desired while galenical preparations (extracts tinctures pills etc) are generally used when there is no urgency No general action may take place if the excretion of a drug is as rapid as its absorption because the effective concentration cannot be maintained

Rate of absorption

Rapidity of absorption is proportional to the rapidity of the circulation and flow of lymph through the part In cases of heart disease where there is stasis in the circulation of the intestine digitalis may be poorly absorbed and this accounts for the occasional failure of digitalis therapy in these conditions For the same reason lesions of the spinal cord delay absorption Vasoconstriction and catarrhal conditions of the intestines may also reduce absorption Excessive distension of the gut decreases the rate of absorption by slowing the blood and lymph flow Although drugs such as arsenic may travel for a considerable distance through dead bodies and strychnine morphine fuchsin epinephrine etc have been shown to be absorbed in frogs with the heart removed absorption normally takes place only when the circulation is intact Deficient circulation delays absorption some absorption however occurs through osmosis and diffusion even in the absence of circulation In the alimentary canal injury to absorbing cells may either facilitate or hinder absorption

8 Absorption by the Blood and Lymph

Most soluble substances are absorbed from the alimentary canal by the blood rather than by the lymph and this is also true of serous cavities Substances such as methylene blue methanamine and some other drugs injected into the pleural sacs appear in urine before they are seen in the thoracic duct All these drugs however may also be detected in the lymph Inanimate particulate matter as well as bacteria in their passage from the tissues to the blood stream go *via* the lymph channels and not the blood capillaries Even from very recent wounds which imply opened blood vessels the above mode of travel holds good Only those substances carrying a molecular weight of less than 5 000 (*e g* cobra venom strychnine) are taken up directly by the blood capillaries Russel viper venom black tiger snake venom diphtheria and tetanus toxins all possess a molecular weight of over 20 000 and are thus carried to the blood stream by lymphatics Recent work seems to have thrown some doubt on the assumption that some toxins can travel up through nerve trunks

A large number of drugs are either not absorbed at all or only in minute amounts Of the common metals only arsenic and mercury are readily taken up and both of these are volatile most of the heavy metals are absorbed so slowly that weeks or months of ingestion may be required to produce poisonous effects Injection into the circulation of the same amount of iron as given by mouth may be attended with serious results The difference in toxicity here is largely a question of absorption

Absorption through the skin in man is very slow though some substances such as methyl salicylate may be rapidly absorbed The skin of young children is more permeable and death has occurred by application of methyl salicylate in this way Absorption occurs more rapidly from regions where the epidermis is thin *e g* axillae groins inner surface of arms and thighs That is the reason why inunctions are given in these regions Potent drugs such as atropine and aconite should be applied with care If absorption is required from the skin the drug should be incorporated with lanoline or lard Lanoline is said to carry the drug to the tissues lard to the skin only and petroleum to the surface of the sl in Absorption occurs quickly from the pleural and peritoneal cavities Hypertonic salt solutions first draw water from the blood and when they are isotonic they are rapidly absorbed

Absorption is delayed by emotional states fear pain and sorrow may seriously interfere with the emptying of the stomach d gestion and absorption Many pathologic conditions delay absorption Absorption of fat is delayed in tuberculosis of the intestines on account of destruction of the lymphatics In extraintestinal tuberculosis the absorption of all types of food materials is very considerably reduced

Some drugs produce their effect because they are not absorbed *e g* some ... of a dr g s l mited by the rate of its excre ... such processes as oxidation

9 Sojourn of Drugs in the Blood

A drug once absorbed into circulation stays in the blood only for a short time The passage of the absorbed or injected substances from the blood into the tissues is a rapid process for diffusible substances and materially slower for colloids Intracellular absorption is a very rapid process again and depends

on the nature of the drug and to some degree on its concentration Toxic doses of arsenic, after intravenous injection disappear completely from the blood in less than 30 seconds diphtheria toxins take 4 minutes, cyanides 2—6 minutes, anti toxins circulate for several hours A group of dyes remain for longer periods in the plasma, another group are rapidly excreted by the urine, and a third group disappear from the plasma, but are not excreted by the kidneys

10. Time Taken to Produce Action

This is often an important question After administration by mouth, a drug may take anything from half to 2 or 3 hours or more before the action is apparent After an intravenous injection maximum concentration in the blood is produced immediately and response may also be immediate In other cases the drug has to be activated in the body before producing its effect as for example is the case with organic arsenicals Reaction between the drugs and the body cells may take time and probably this is the reason why even after intravenous injections atropine or ergotoxin may take five to fifteen minutes before producing effect

Delayed action

Certain drug actions are produced only after the drug has been in the body for prolonged periods Radio active compounds are examples of this class, and may produce death after a latent period of many years With thyroxin dosage and duration of action is an important factor, a single large dose may produce little deleterious effects but the same quantity given in divided doses over a number of days may produce death In case of lead, a single large dose is harm less but repeated small doses produce poisoning

A single dose of a drug may produce ill effects the consequences of which may not be seen for a long time In case of mercury diethyl for example the effects of a single [illegible]
till after latent perioc[illegible]
symptoms In case of [illegible]
a few days the toxic [illegible]
three months or more, [illegible]
In case of X rays and radium, erythema or burns may appear only after some days

11. Distribution of Drugs in the Body

Storage in tissues

This is not a uniform process Drugs accumulate particularly in certain cells according to their permeability and physical and chemical affinities These influence their action either by bringing them in contact with reactive tissues or storing them in places where they may be inactive. Iodine is stored in the thyroid gland as iodothyrin, bones retain earthy metals and fluorides, heavy metals are deposited as loose organic compounds in the liver and the spleen mercury forms a loose globulin compound, with arsenic a more stable nuclein combination occurs in the Liver, bone marrow, skin etc, chlorides bromides and related ions accumulate in all organs but mainly in the skin and the blood Little is known about the distribution of organic poisons, mainly for want of suitable assay methods

12 Changes in Drugs during Absorption

The majority of drugs are altered in the body by processes of oxidation, reduction hydration dehydration or decomposition, by storage in certain organs, or combination with other substances, toxic drugs are rendered harmless This

process of detoxication is of very great importance as it renders the continuous administration of drugs (in most cases in increasing doses) an absolute necessity If it were not for this power of the organism to destroy and remove poisons *and thereby to recover from its action*, all therapeutic uses of drugs would have been an impossibility On the other hand, the alteration of the drug by the body may result in the formation of more toxic substances (nitrites) or the drug may *be rendered more effective therapeutically* as is the case with pentavalent organic arsenicals The digestive juices destroy some organic poisons by hydrolytic changes (glucosides, proteins and anti toxins) They are also necessary to saponify and liberate *the active constituents of insoluble esters (phenyl salicylates)* The acidity of gastric juice is of importance in the solution of bases

The tissues play a part in decomposing toxic drugs Strychnine morphine and many *other alkaloids are partly oxidised in the tissues and thus rendered inert* Many organic acids, alcohols and formaldehyde are detoxicated by oxidation The organic compounds of metals (*e g* cacodyles) only develop their metal action after oxidation The thyroid gland is said to play an important part in destruction of poisons in the body and its *excision increases the toxicity of many poisons* The liver is believed to be a great disin toxicating organ acting partly by destroying poisons and particularly by storing them It possesses greater power to destroy drugs than other organs though alkaloid destroying fer ... also n small *quantities That is the reason why the same* ... *o one of the mesenteric veins than when given* ... to be the case with curare strychnine mor ... d the metals Perfusion of alkaloids glucosides ... decreases their toxicity Perfusion through excised muscle also produces a certain amount *of detoxication but this is weaker than that* is produced by the liver Excision of the spleen is said to increase the toxicity of most alkaloids but not all Phagocytes accumulate and detoxicate many poisons especially the colloids The serum of atropine resistant animals (rabbit) destroys atropine

The liver as stated above defends the body against toxic substances absorbed ... can detoxicate many substances and those wh ch ... nting them from producing deleterious action on ... s fixation of arsenicals in the process of which it ... or excrete drugs ... aried character ... action of such ... to produce and ... *When the action* ... reted rapidly or

13 Adsorption

Adsorption comes from the Latin word '*Sorbere* meaning to suck It is the power possessed by certain substances of retaining on their surfaces gases, liquids and solids either in solution or in the colloidal state *One substance* here becomes a part of another and remains in a state midway between mechanical *mixture* and chemical combination This phenomenon plays a very important part in the action *of drugs The disintoxication is sometimes* carried out through adsorption thus pilocarpine is detoxicated in excised intestine by digestion with serum, but it may be fully recovered from it in active form by extraction with *acid or alcohol showing* that it was not destroyed The nature of adsorbing substances is not known but it is found in abundance in rabbit's serum less in that of cats or oxen, and it is absent in dog's blood

14 Excretion of Drugs

The main channels of excretion are the kidneys and bowels, and with volatile drugs the lungs The sweat and for that matter other secretions play a com paratively minor part *The relative importance of different channels varies for* each drug The excretion is proportionate to the circulation of the blood and

may be increased by factors which stimulate it The excretion of certain drugs is limited by their being in the body in the form of combinations the elimination of these is favoured by substances which displace them in the compounds (excretion of iodides is increased by giving chlorides)

nides borates phenol
The quantities thus
the point of view of
elimination but they help to explain certain skin conditions which accompany their administration Excretion by saliva is limited to iodides potassium ammonium mercury lead menthol guaicol and some alkaloids (morphine and quinine) The excretion generally begins within 20 minutes and lasts for nine hours

15 Passage into Cerebro-spinal Fluid

Selective absorption

The lining cells of the choroid plexus exercise selectivity in letting through various substances into the cerebro spinal fluid This is the reason for such differences in the concentrations of various normal chemical constituents in the plasma and the cerebro spinal fluid For a number of compounds such as the citrate and iodide of sodium and also for colloids of the plasma the choroid plexus lining is a complete barrier Bile pigment also even when present in the plasma in high concentrations do not penetrate into the cerebro spinal fluid except in negligible quantities Many substances on the other hand pass from the serum into the cerebro-spinal fluid quite easily as for example morphine strychnine pilocarpine volatile anaesthetics alcohol bromides salicylates and the basic dyes like toludine blue pyronine safranine and neutral red Sulphonamides are the latest addition to this group of drugs their concentration in the cerebrospinal fluid being about 75 per cent of that in the plasma

their trans t barred

16 Passage to Fœtus

Chloroform ether alcohol chloral ethyl bromide scopolamine quinine atropine morphine arsenic mercury potassium iodide potassium bromide carbon monoxide salicylic and benzoic acid phloridzin nitrates urea methylene blue pass into the fœtus if given to mother The placenta acts as an ultra filter towards colloids The colloidal dyes and proteins do not pass into the fœtal circulation

17 Toxic Effects

Definition of poison

If drugs are given in adequate doses they produce therapeutic effects but if larger doses are given they act as poisons Poison comes from the Latin word *potio* meaning a draught By poison is meant any substance administration of which will injure health or cause disease These effects may be immediately manifested or they may take some time to occur Toxicology comes from the Greek word *toxikon* meaning a poison It deals with the symptoms diagnosis, treatment and detection of poisons As a large number of the drugs used in the treatment of disease are potent substances their dosage and the length of period during which they are to be administered should be very carefully considered The safety factor in dosage is often assessed by considering the

Safety factor

ratio of therapeutic dosage of the particular drug to its minimum lethal dose As minimum lethal dose is not a stable definite figure it is preferable to base calculations on the average or the median toxic dose The physician should be clear about the chances of a particular dosage producing toxic symptoms As a rule it is not justifiable to use a dose which carries even a 1 in 1 000 chance of producing serious or fatal toxic effects Even when the dose is considered safe and this is specially true of powerful remedies the final adjustment in the dose should always be governed by the response elicited from the patient who should be under careful observation

18 Chemical Constitution and Physiological Action

If action of drugs could be anticipated by the knowledge of their chemical formulae the task of discovering effective remedies for diseases at present without specific cures would have been considerably eased At present new remedies are hit upon mostly by mere coincidence and sometimes hundreds of compounds are turned over before one can be found which affords reasonable chances to merit a clinical trial

Even very slight differences of chemical constitution in seemingly alike drugs may mean a material divergence in their action

The laevo rotatory isomer of epinephrine is seventeen times stronger than dextro rotatory isomer On the other hand drugs having a very dissimilar constitution may have similar actions Drugs prepared for one action may produce action of a different kind altogether The search for remedies is therefore a laborious process of trial and failure

CHAPTER II

CONDITIONS MODIFYING THE ACTION OF DRUGS

DOSAGE—ACCUMULATION OF DRUGS—HABIT—SEX RACE AND CLIMATE—TIME AND FREQUENCY OF ADMINISTRATION—IDIOSYNCRACY SUSCEPTIBILITY AND TOLERANCE—INDIVIDUAL VARIATIONS IN THE ABSORPTION OF DRUGS FROM THE GASTROINTESTINAL TRACT—SYNERGISM AND ANTAGONISM—EXTERNAL FACTORS—STANDARDISATION AND BIOLOGICAL ASSAY

1. Dosage

By dosage is meant
or after repetition T
is called the *maximum*
weight and it is ration

Definition

In children the dose is usually given according to age

Dosage in Children

Many practical rules have been devised for calculating the doses for children when the adult dose is known

(*a*) Young's rule $\text{adult dose} \times \dfrac{\text{age}}{\text{age}+12}$

(*b*) Cowling's rule $\dfrac{\text{adult dose} \times \text{age at next birth day}}{24}$

If prescribing 24 doses all that is required is to multiply the adult dose with age of the child in years

(*c*) Bush's rule Multiply the age by 5 this gives the percentage of the adult dose

(*d*) Dilling's rule $\text{adult dose} \times \dfrac{\text{age}}{20}$

In this connection Clark has formulated a method of dosage for a person of known weight— $\dfrac{\text{adult dose} \times \text{weight of person in pounds}}{150}$

150 lb is taken as average weight of an adult person This method though useful is not always feasible as it is impossible to weigh a patient lying in bed A rough estimate of the probable weight can however be made

A single dose may be given or divided doses may be administered (1/4 gr calomel every half hour till 2 to 4 grains are taken) Repeated doses may be given (1) to have effect just at the time of administration or (2) to have continuous effect (digitalis for disordered heart) A drug may have different effects according to the dose in which it is given *e g* ammonium carbonate is an expectorant in 3—10 gr doses and an emetic when 30 gr are given.

2 Accumulation of Drugs

Cumulative action

and increasingly powerful effects
Such drugs are called cumulative

Accumulation is liable to occur also in case of metallic drugs which cannot be destroyed or detoxicated in the body and which are as a rule slowly excreted mercury lead arsenic bismuth, etc are examples of such drugs It may also occur when the excretion is decreased or suddenly stopped for some reason *e g*, when there is nephritis or a sudden solution and absorption of a sparingly soluble drug owing to some change in intestinal content Successive doses of the drug may remain unabsorbed in the alimentary canal

actions and responding to them more

3. Habits

Habit usually lessens the effect of drugs to some extent ... phine or opium need bigger doses of these drugs, need larger doses of hypnotic and anaesthetic drugs I after continued use, as in case of the purgative cascara ing drugs tolerance may be largely psychic The ner reactions so as to adapt them to drug environments When this environment is abruptly altered by withdrawal of the drug there is generally extreme discomfort, resulting in craving and great nervousness, constituting abstinence symptoms Functional habituation, when acquired for a particular drug, may hold also for other drugs having a similar action

4. Sex, Race and Climate

Women are more delicate and lighter than men and need three fourths to four fifths of the dose of men Idiosyncracy occurs more often in the female sex, during the menstural period certain drugs are not advisable (*e g*, quinine may cause excessive bleeding) Pregnancy and lactation should also be taken into consideration as some drugs are excreted in milk, while others have action on the gravid uterus

Various species of the same family show remarkable difference in their reaction to drugs Different organs of the same animal exhibit diverse reaction to drugs such as adrenalin atropine, pilocarpine, etc Racial differences may also play a part in the action of a given drug

system

5. Time and Frequency of Administration

This is of importance, *e g*, saline purgatives act most rapidly on an empty stomach after a period of fasting so they are usually given in the morning before breakfast. The more slowly acting purgatives are given at bed time and half an hour before meals Irritant drugs, such as arsenic or iron, are best given after meals, when they become well diluted with the stomach contents and come in contact with the stomach wall in lesser concentration and do not irrate it, quinine sulphate is best given 1½ to 2 hours after ... the contents of the stomach are acid ... time, digitalis preparations are best ... rific drugs are most effective at the ... if the patient is not in bed and is up and about Sodium bicarbonnate is given on an empty stomach because if given during the digestive period, it neutralizes the hydrochloric acid of the gastric juice

Relationship between the time of administration of a drug and meal time may influence not only the rate of absorption but also may modify its action. Given on a full stomach the absorption is slower than when given some hours after meals, if local action is desired on the stomach, the drug should be given before meals Whenever possible a purified standard preparation should be used

Frequency of administration is important as drugs are rapidly oxidised, destroyed or stored in the tissues or eliminated through secretions or excretions The rapidity of destruction determines the frequency with which they should be administered The speed or rapidity of administering drugs may mean difference between life and death

6. Idiosyncracy, Susceptibility and Tolerance

No two individuals respond to drugs in an identical manner Drugs may exert an unexpected effect either by having an unusual action or failing to produce ordinary action The term idiosyncracy is applied to peculiar, exceptional reactions to the effect of drugs Fortunately only a small minority of individuals react to certain drugs in an entirely abnormal manner Acetylsalicylic acid, for example, in such individuals, may produce extensive urticarial eruption or even œdema of the mucous membrane of pharynx and

larynx, giving rise to serious symptoms There may be quantitative hyper-susceptibility to ordinary actions of drugs, so that side actions, which are ordinarily negligible, become greatly accentuated Neurotic individuals are subject to psychic exaggeration or modification of drug effects through fright, excitement or suggestion. They are frequent causes of disappointment both to the physician and the patient and may give rise to excessive action from what has been thought to be a moderate dose

Idiosyncracy.

...ncracy in which the patient reacts to ...ma and spasm of smooth muscles, ...nerally hereditary but not congenital, *i e*,

while spinal reactions predominate in lower vertebrates Rabbits are incapable of vomiting, therefore, they cannot be affected by emetics Normal resistance may be due to *destruction of the poison, e g, atropine by serum of rabbits Differences of absorption* and excretion also come into play There are many factors, however which cannot be satisfactorily explained It should not be forgotten that abnormal reactions following the administration of drugs may rarely be due to the presence of impurities

Tolerance

Some animals and men fail to react to drugs even when given in considerable doses and this phenomenon is known as tolerance which may be natural or acquired, *i e* developed by repeated administration of a drug Natural tolerance may be due to the power of the tissues to neutralise poisons Thus carnivora can stand large amounts of

Mechanism

Tolerance versus immunity

Acquired tolerance has already been considered under HABIT Tolerance is usually limited, not absolute Any condition which lowers the general resistance of the animal increases its susceptibility to the poison (frog in tepid water) Tolerance differs from immunity in that anti toxins are said to be formed in the latter Anti toxin formation, however, is an instance of acquired tolerance It was supposed to be confined to proteins, but it appears to exist also towards certain glucosides (toad stool and snake venom) It does not occur with alkaloids It is doubtful if any chemical substances except *proteins* produce anti bodies.

It will thus be seen that methods by which the body can protect itself against drugs are varied and that tolerance is a result of complicated factors

Drug Addiction is a separate problem but is dependent on tolerance. Tolerance may, however be produced quite independently of addiction The subject has been dealt with in detail later

7. Individual Variation in the Absorption of Drugs from the Gastro-intestinal Tract

In order to understand individual variations in the absorption of drugs it is essential to appreciate the digestive functions of different parts of the alimentary tract, because

Physiological considerations

uniform consistency by chemical and mechanical means The digestion of food is started here and the contents are passed on to the middle portion.

The middle portion begins in the lower part of the duodenum and extends to the ileo cæcal sphincter Its functions are to complete the digestion of food and to absorb as much as possible Nearly 90 per cent of the absorbable substances in a meal are taken up here

The lower portion consists of the cæcum the colon and the rectum Its functions are to complete absorption to store and to periodically excrete the indigestible residue. The contents of the small intestine enter this protion in a fluid state, and are reduced to a semisolid consistency Certain reflexes are set up periodically and the contents are expelled. Absorption from the rectum and colon is small and their utility from the point of view of nutrition or medication is very limited

The main factors concerned in individual variability in the absorption of drugs may be grouped under three headings —

(a) *Variations because of physiological factors*—The most ancient the most natural and even now the most widely used method of administration of drugs is by the oral route Its chief advantages are undoubtedly from the point of view of the patients who can make use of medicaments without the intervention of the doctor or any other person A majority of the drugs given by mouth reach the stomach without much altera tions on account of rapid passage through the mouth, the pharynx and the œsophagus No appreciable absorption takes place even from the fundus of the stomach It may be stated here that in case of some drugs considerable absorption may occur from the mucous membrane of the mouth, and this method is adopted in case of some diffusible drugs (e g

push the contents through the pyloric
istric juice The passage of a drug through the stomach may thus take from a fraction of a minute to more than two hours

considerably delayed Absorption of a drug from an empty stomach is often irregular specially if it is irritant, as it may reflexly cause closure of the sphincter and thus prevent its reaching the absorptive surface of the duodenum

Circulation of blood in the gastro-intestinal tract has considerable influence on absorption Absorption is quick when the circulation is normal, it is slowed when it is hampered by such factors as vaso-constriction, catarrhal conditions of the mucous membrane etc. If the physiological processes regulating the activity of the gastro-intestinal tract are borne in mind it would be easy to insure either slow or rapid absorption within certain limits

(b) *Variability because of physical and chemical factors concerned*—The pheno-
all actively
which is not
of the cells
endows the
or rejection
or example
ergo normal

protein digestion

The rate of absorption of a drug is modified by the solvent used. For instance alcoholic solutions are r lutions probably because of the greater diffusibility bstance is in the protoplasm the more quickly it is substances such as gums, resins oils, kaolin, etc when absorbable materials (e g salts alkaloids e the rate of their absorption may be so much slowed that no action occurs the rate of excretion being as rapid as absorption

The concentration of solutions affects the rate of absorption in conformity with the laws of osmotic pressure Saline solutions such as magnesium sulphate which are little absorbed themselves may prevent the absorption of readily absorbable drugs Astringent substances tend to lessen absorption Solids are not suitably altered by the intestinal juices and are not absorbed except through the phagocytes, they may even then be deposited in the lymphatic tissues They exert no action unless dissolved by body fluids

Effect of disease

(c) *Variation in absorption due to disease*—When the normal functions of the stomach are deranged on account of disease considerable changes occur in the absorption of drugs Thus in case of shock absorption is considerably decreased and may even stop altogether Slight irritation of the gut which does not cause injury increases absorption but absorption is decreased and may be totally inhibited when the gut is injured

In febrile states it would not be safe to estimate the probable rate of absorption In a sick person the rate of absorption may differ considerably from that which occurs in health Often absorption is considerably reduced when there is general reduction of vitality, the lower resisting power of the body occuring in chronic constitutional diseases retards absorption If the intestines themselves are diseased they allow much more rapid diffusion of proteins toxins and ferments than healthy intestines but absorption of drugs may be adversely affected

Effect of gastro intestinal lesions

It is not surprising therefore that the same drug given to two different patients under similar conditions for the same symptoms, may behave entirely differently, and on testing the urine one patient may show the presence of the drug and the other may not The reason of this variation is not far to seek An analysis of the records of patients admitted into the Carmichael Hospital for Tropical Diseases Calcutta showed that in as many as 60 to 70 per cent of patients the gastro intestinal tract was involved

Helminthic infestations

Dysenteries and diarrhoeas

Another important factor which should not be lost sight of is that the rapid passage of a drug through the small intestine, where absorption usually takes place, occurs in chronic diarrhœas and dysenteric conditions X ray examinations with barium meal show that the meal in these cases hurriedly passes through the small intestine, and in a very few hours less than five usually, it reaches the pelvic colon no trace being left in the small intestine Drugs therefore are not allowed sufficient time for absorption Besides these conditions the mucous membrane of the gastro-intestinal tract is not normal in a large percentage of patients in the tropics and peptic ulcer disease of the liver and gall bladder and pathological appendix, colitis, etc, are frequently met with The absorption of drugs in such cases may be far from normal and may show considerable individual variations

The importance of these factors was emphasised during clinical trials of different anti malarial drugs Results with even such potent drugs as plasmochin and atebrin, were so variable that it was not till the excretion of these drugs in the urine was studied side by side with their effect on the malarial parasites, and clinical symptoms in a large series of cases, that the cause of these discrepensies was understood. It was found that in some cases the absorption of such drugs as quinine and atebrin, was considerably delayed, in other cases it was very small and yet in other cases there was no absorption at all What is true of atebrin and plasmochin holds good in case of other drugs also Every medical practitioner is familiar with the wide individual variations in response to drugs *No two individuals respond to any drug in an identical manner* and a small minority may react to certain drugs in an wholly abnormal manner Extensive data in this connection has been gathered from biological standardization of drugs with different stocks of animals and large variations in dosage and response are found. If this is the case with healthy animals, it is not surprising that large

variations occur in disease and particularly when the disease affects the gastro-intestinal tract *The physician should carefully consider* ... before administering them and when expected results ... vations entertained over many years by the author, ... to be responsible for variability in the absorption ... tract *The practitioner in tropical and sub tropical climates* should bear these in mind —

1 Absorption of drugs is considerably modified in acute and chronic *inflammatory* conditions of the mucous membrane of the gut

2 Hypoacidity of the stomach which is often met with in chronic dysenteric and other infections has considerable effect over the absorption of drugs

3 Rapid passage of meals through the small intestine generally, and through its upper part particularly where these drugs are usually absorbed hinders absorption. This is quite commonly met with in amœbic and bacterial dysenteries and affections of the liver

4 Drugs *administered in form of tablets which may not be properly constituted.* Some of the ingredients used may prevent their disintegration before reaching the part *where absorption of drugs takes place In some cases the tablets may not disintegrate* at all and may pass through the gut unchanged

8. Synergism and Antagonism

A drug exerts its usual activity much more easily if it is given with some other drug of the same class and it is found that combination of two drugs having the same action will give a result which one alone will not produce, however large the dose might be Such drugs are called synergists or mutual helpers and the phenomenon is known as synergism In some cases new actions develop by the reaction of drugs with each other, with the production of new compounds (acid renders the basic salts of bismuth soluble and toxic)

Synergism of drugs was responsible for combination therapy which had the idea of securing summation of the desirable effects of several drugs, the side actions usually do *not increase and in some cases they are neutralised Formerly this form of therapy* ... shot gun prescriptions were given with the idea that some at least of the ... of drugs

The best examples of synergism are seen in the group of narcotics in the ... of alcohol ether and chloroform the effect is simple summation but in case of *morphine* and scopolamine there is considerable augmentation of effects Again an injection of magnesium sulphate *considerably helps the action of ether in the production of general* anaesthesia A mixture of purgatives, *e g*, calomel, jalap and colocynth, act better than any one of them alone

The synergism may be produced by one drug modifying the penetration of the other into the cell, altering the chemical affinity or attacking the cell from a different point of view Magnesium potentiates urethane and ether potentiates chloral or morphine, by favouring their distribution in the central nervous system

On the other hand a drug may lose a part or all of its action because of some agent which has the opposite physiologic effect Such opposing agents are called antagonists *and the phenomenon is known as antagonism There are examples of* antagonistic substances being manufactured by the body itself (insulin and adrenalin) The antagonism between drugs and poisons when this depends on the antagonistic innervation of certain organs is easy to understand (*i e*, vasodilators and vasoconstrictors) *Much more difficult to understand* is the antagonism by which one drug overcomes the effect of another in the same cell without the aid of physiological mechanism This may be brought about in two ways —

(1) By chemical changes or combination as in case of free acids and alkaline carbonates oxalates and lime salts

(2) By true antagonism, as in case of atropine and muscarine, which is of truly physiologic nature, for these two drugs have no chemical affinities for each other, but produce directly opposite effects on the same organic element The action of potassium

Reciprocal antagonism

[illegible] together in proper
[illegible] mplete reciprocal
[illegible] hile it is possible
[illegible] to bring about
[illegible] that combination
[illegible] cells may be
restored again and poison washed out from them if bathed with blood which is free from the poison Reciprocal antagonism between calcium and magnesium and sodium and potassium is clearly demonstrated in living organism for the tissues can maintain their normal function, particularly their normal excitability only when these kations are present in their correct relative proportions

Antagonistic drugs may act, (*a*) on the same structures *e g*, bromide and strychnine on the spinal cord, caffeine and alcohol on psychic and motor centres in the cerebrum, pilocarpine and atropine on the vagus nerve endings, (*b*) on different structures, *e.g.*, digitalis slows the heart by stimulating the vagus centre atropine prevents this by depressing the vagus nerve endings Adrenalin contracts vessels by stimulating the vasoconstrictor fibres while nitrites relax them by acting on the muscle fibres

9. External Factors

Some drugs are more potent in the presence of ultraviolet rays than in dark Temperature is an important factor, the effect of most drugs being more intense at higher than at lower temperatures Atmospheric pressure is another factor, thus carbon monoxide does not kill if *operating under a pressure of* several atmospheres Bacteria and enzymes may also play an important role

10. Standardisation and Biological Assay

Chemical and physical assay

In order [illegible]
States Pl [illegible]
This sect [illegible]
way their [illegible]
compositio [illegible]
in case of most of the preparations Physical assays are carried out in form of saponification values, refractive indices optical rotation, specific gravity iodine values, and melting points

Biological assay

In case of a number of drugs however, the active principles are either unknown or are of such a complicated nature that ordinary methods of chemical assay are not applicable Such drugs are assayed by biological methods The principle underlying is to estimate the strength of the preparations by determining the minimum lethal dose to animals under standard conditions of weight and species In other cases the standardisation is carried out by noting the physiological effect produced on some organs such as heart uterus ovaries etc According to the British Pharmacopœia the following preparations are assayed by biological methods —

Neoarsphenamine and sulpharsphenamine, digitalis (powder and tincture) strophanthus (tincture), strophanthin, insulin, pituitary (posterior lobe) extract old tuberculin, diphtheria antitoxin gasgangrene antitoxin anti dysenteric serum tetanus antitoxin staphylococcus antitoxin, anti pneumococcus serum vitamins A B C and D

CHAPTER III

MODES OF ADMINISTRATION

INTRODUCTION—LOCAL APPLICATION ON SKIN, ON MUCOUS MEMBRANES, IONIC MEDICATION—*ORAL AND RECTAL ADMINISTRATION—ADMINISTRATION OF DRUGS BY INJECTION* SUBCUTANEOUS OR HYPODERMIC ROUTE, INTRADERMAL ROUTF INTRAMUSCULAR ROUTE, INTRAVENOUS ROUTE, OTHER ROUTES

1. *Introduction*

By mode of administration is meant the way in which a remedy is to be used Remedies are given to obtain either direct local action a remote local action a systemic, or general action.

The direct local action of a drug is exerted at the place at which a drug is appl ed *e g*, skin, nose, urethra, etc Locally, drugs may act by protection, irritation, or depression of sensory nerve endings or oher tissues Many drugs act locally only, others like strychnine, exert little or no effect at the point of application, but exert a marked general effect Local remedies may or may not require to be absorbed, *e g*, bismuth subnitrate for an irritated stomach talc powder for skin which is chafed

Remote or indirect action is an action elicited on organs away from the site of application Such action of drugs may appear (*a*) after its absorption into the circulation, *e.g*, of strychnine on the spinal cord, pilocarpine on the secretion, (*b*) without actual absorption, *e g*, irritation of the skin blisters or cold applications *influence the rate of the heart, indirectly through the central nervous system* Sometimes the effect of a drug is manifested as it is being excreted *e g* irritation of the bowels and kidneys by perchloride of mercury as it is passed out *via* the colon and the urine, antiseptic action of urotropine as it is eliminated in the urine

The general action is one that cannot be fixed in any particular tissue *i e*, the action of many tonics and sedatives

The effect of a remedy depends largely on the way in which it is given, *i e*, adrenaline given by month has a local action on the stomach only, while if given hypodermically or intravenously it produces an enormous rise of blood pressure A dose of saponin by the mouth is perfectly harmless, but it gives rise to poisonous symptoms if given under the skin Some tissues an ... than others there fore larger quantities of the dr ... in a given time For instance if a poison which is ... little of it will exist in the blood and tissues at a ... , while if it is rapidly absorbed by some other method of administration, even a small dose will exert some action before it is excreted, *e g*, potassium salts given by the *mouth are not* poisonous in large quantities, but when given hypodermically or intravenously they produce toxic effects on certain organs

... the body or the place to which it is ... secured, *i e* whether the action is to ... orption is desired or whether there is ... etc

2. Local Application

Locally drugs may be used to protect surfaces for producing reflex effects for antiseptic or *stimulant purposes*

(1) On Skin

On the skin drugs may be applied in various vehicles *If it is desired the drug* should penetrate deeply or be absorbed it should be mixed with animal or vegetable fats The reason is that although the lower layers of skin absorb readily the stratum corneum of the ... ble to most s bstances The absorption takes place through th ... fatty matter Increased vascularity of t ... quickly the absorbed drug Where local eff ... may be used Oils and ointments delay ... s phenol mustard oil etc

Local application to the skin has to be used for producing general effects in those cases where the stomach must be avoided and the subcutaneous method is not practicable, *e g*, inunction of mercury. The objection to this method is that (1) absorption is uncertain and consequently exact dosage is impossible, (2) the absorption is greatest where the skin is most delicate (axilla loins, inner surface of the extremities) Absorption is aided by rubbing

Watery solutions as a rule are not absorbed from the skin but when the solutions are brought in intimate contact, certain salts may be absorbed. Skin is capable of absorbing sulphuretted hydrogen and other gases Application of watery solutions to the abraded skin or open wounds is however, quite a digerent matter Absorption under such conditions takes place readily and the rate of absorption is practically similar to that obtained by subcutaneous injections Chronic and callous ulcerations with defective circulation are, however, poor absorbing surfaces

(2) On Mucous Membranes

Absorption from mucous membranes

Drugs can be applied locally to surfaces other than skin *e g* mucous membranes The conjunctiva absorbs readily, so that apart from local action a systemic effect of drugs may, sometimes, be produced, *e g*, atropine A few milligrams of apomorphine in the conjunctival sac of a dog produce vomiting The vagina absorbs freely and clinical poisoning may be produced by giving the drug in the form of douches The uterine cavity also provides a very good absorbent surface The urethra absorbs readily and frequent poisoning has occurred from application of local anæsthetics The urinary bladder absorbs poorly, drugs like strychnine, apomorphine morphine etc, are quite harmless when given by this way The ureter and renal pelvis absorb fairly well

[illegible] rapidly if these are introduced [illegible] ater given into the trachea of a [illegible] no trace of water being found, [illegible] ue Rabbits can receive 30 to 40 [illegible] into the trachea If the fluid is injected more rapidly than it is absorbed it fills up the alveoli and produces asphyxia This route of administration is, however not used in therapeutics on account of the danger of asphyxia

Sprays

Sprays are finely atomised solutions and are inhaled for their local action on the mucous membrane of the nose, pharynx and larynx They must not be too irritant To reach the lower air passages they should be deeply inhaled with the nostrils closed, the mouth widely opened and the tongue slightly protruded In the treatment of asthma 1 in 100 adrenalin spray introduced by an atomiser is used with benefit Small quantities 2 or 3 c cm of oily solutions (*e g* menthol) may be injected directly into trachea through the glottis They are then distributed by respiration Powders are also frequently blown on to a surface *e g* boric acid into the ear or relatively inaccessible parts and this is called insufflation

Inhalations

Inhalations are used for gaseous medicines such as anæsthetics oxygen, etc The effect depends on the concentration of the gas and the time during which it is administered The action is most rapid as they reach the blood stream quickly The capillary surface of the lungs which is only separated from the alveolar air by a single layer of flattened epithelial cells is wonderfully adapted for absorption of volatile substances into the blood The chief advantage of this route of administration is the possibility of controlling the amount of drug at any desired time The effect also disappears quickly after the drug is discontinued

A recent [illegible] for some time [illegible] 4 ccm a day for 4 to 6 [illegible] recent use of inhalation [illegible] sal inhalations of the latter [illegible] effect is desired (*e g* hay [illegible] lrenaline

Local

Inhalations are used for local action also These can be effectively employed by evaporating the substance with steam either by placing it on boiling water and inhaling it through

mucous membrane and the drug is deposited at that area Even with deep inhalations the *vapour does not go beyond the larger bronchi* The respiratory movements however tend to distribute the material widely through the lungs In many affections of the nasal and upper respiratory passages this method is very commonly used

(3) Ionic Medication

By this is meant the administration of drugs for either local or general effects through the skin and by the use of electric current Proper manouvring of cathode and anode is all that is necessary to lead the dissociated ions of electrolytic solutions into the tissues Superficial or even deep ionisation may be used when superficial effects are desired but *for systemic effects deep ionisation is required*

Negative charges (acid radicals) are attracted by the anode and positive ones (basic radicals) by the cathode For instance, in the case of potassium iodide (potassium has a positive charge whereas iodine has a negative one) when the drug is applied to the surface of the body by the anode *the cathode being placed at any other point, the* potassium (+) will collect at the cathode (—) after penetrating the tissues whereas iodine (—) after dissociation will collect at the anode (+) Similarly iodine can be led into the tissues by applying the drug by the cathode The quantity of ions which can be taken into the tissues is dependant upon the strength of the current used.

When salts of organic bases are being used for ionic penetration they should be applied at the anode as in their case the basic radical is the one which is generally [illegible] (*e g* aconite cocaine morphine etc) In the case of inorganic [illegible] s) acid radical is usually the one [illegible] le *The therapeutic field for ionic* [illegible] to topical applications and may be [illegible] For ionic medication in human [illegible] of active electrode for 15 to 20 [illegible]

3. Oral and Rectal Administration

Oral administration is the most ancient method and is still the method of choice with most drugs Drugs whose general action is desired after absorption are generally given *by this way but sometimes drugs may be given for their local effect by this route* also (*e g*, bismuth and emetics for their action on the stomach vegetable purgatives on the intestines)

Some drugs give rise to disturbances of digestion when given by the mouth This can be avoided by giving them in the form of pills coated with keratin in capsules or cachets so that they will not get dissolved in the stomach or they may be given when the stomach is full so that they are diluted. Absorption mainly takes place from the small intestines

Rectal administration may be used to avoid the action of a drug on the stomach and the small intestine The rectum on account of its profuse vascularity and venous plexuses is a very good absorbing surface for many soluble substances so that effects are often more prompt and more marked than with the oral method Absorbed substances moreover do not all pass through the liver where they are liable to be destroyed The drug is given in the form of an enema or suppository Enemata when given for absorption should be as small as possible (2 ounces) and not irritant The rectum should be washed out with warm normal saline before they are given About twice the dose given by the mouth is necessary to produce the usual effects.

The rectal administration of drugs has been practised since the time of Galen and although its utility is limited *it still occupies a very large place in therapeutics* As many drugs are fairly well absorbed from the rectal mucous membrane there is a growing idea that this route of administration may be resorted to in supplying nutriment to the system whenever occasion demands it

The use of *nutrient* enemata or suppositories containing food meterials is based on the assumption that absorption takes place from the rectum and the large bowel The absorption of foodstuffs from the rectum is however very limited Physiologically the rectal mucous membrane is unsuited for the purpose of digestion and absorption of nutrient material The main digestion of food as is well known takes place in the small *intestines. The pancreatic juice* furnishes powerful ferments which digest starch (amylase), fats (lipase) and proteins (trypsin) The bile renders important assistance in the digestion of fats The secretion of the mucous membrane of the intestines (succus

entericus) also possesses an important digestive function through its ferment 'erepsin' After the digestion is completed, absorption takes place through the highly specialised epithelium of the villi of the intestinal mucosa Practically the whole process of digestion and absorption is completed in the small intestines before the material is transferred through the ileocaecal valve into the large intestines In the large intestines absorption of water chiefly takes place 'Erepsin' is the only ferment present which can break down proteoses and peptones only into the simpler amino-acids The villi are widely different and are unsuited to the absorption of nutrient material

Protein absorption

The bacterial contents of the large intestines may play a part in digesting certain materials which are resistant to the action of the digestive juices in the small intestines, *e g*, cellulose, but this digestion is very insignificant in human beings

Some observers have stated as a result of comparative study of the nitrogenous metabolism in patients on rectal feeding that quite large amounts of protein are absorbed Recent observations have, however, demonstrated that this statement was based on fallacious experimentation and cannot be taken at its face value Boyd has shown that nitrogenous equilibrium could not be obtained during rectal feeding even in those who were accustomed to a diet poor in nitrogen Laidlaw and Ryffel estimated the nitrogenous output in a case of rectal feed... [illegible]
equal to that obt[illegible]
was not taking [illegible]
giving nutrient e[illegible]
liquor pancreatici [illegible]
accurate criteri[illegible]
loss of nitrogen from the rectal washings, which method was employed by previous workers. It was found that the nitrogenous metabolism was hardly affected

Carbohydrate absorption

[illegible]
in 15 ounces of tap water is used six hourly with daily irrigation of the bowel four hours after the last dose Different observers have claimed that nearly 67 to 100 per cent of the carbohydrates are absorbed

Fat absorption

As is well known fats are never absorbed *in toto* but are first broken up into glycerin and fatty acids through the agency of an enzyme 'lipase' This ferment is not present in the large intestines [illegible]
may under exceptional [illegible]
Even if the pancreatic [illegible]
tion of fats is not sat[illegible]
absorbed than other f[illegible]
not absorbed and most [illegible]
any advantage to the [illegible]
tion of fats takes place recent observations definitely negative the suggestion Practically no fat is absorbed from nutrient enemata by the large bowel

Salts and water

[illegible] ely absorbed from the large intes[illegible] are probably due to these ingre[illegible] ation of food for a consider[illegible] tion of 10 oz enemata of plai[illegible] has been advocated

It will therefore be seen that [illegible]
not very sound It is only a poor substi[illegible]
small intestine is completely cut off It [illegible]
through the ileocaecal valve and be absor[illegible]
case of duodenal fistula that some quan[illegible] ...ich an exceptional circumstanc[illegible]
[illegible]

It appears possible that better results might be obtained if the proteins are completely broken down into amino-acids, the form in which absorption normally occurs.

By allowing pancreatic extract to act on milk for twenty four hours and using the digeste material as an enema, decidedly better absorption takes place.

ntages

It is true that water, . . . el in suff cient quantities to tide the . when fo some reason or other, tl . are, how ever, certain disadvantage onvenienc and difficulty caused in keeping the patient in a clean condition, there are certai symptoms which require attention Excessive thirst, persistent vomiting reflex secretion o gastric juice, *parotitis due to ascending infection* of the salivary ducts, etc, are some o the unpleasant complications These can be avoided to a large extent if proper nursin facilities are available

4. Administration of Drugs by Injection

This method is of comparatively recent origin, but its use is being rapidly extended

ges

Irritant drugs should not be given by injection into the tissues, as this may caus great pain and swelling and sometimes suppuration even when all precautions regard ing sterilisation are taken, *e g*, *turpentine*, and *digitalis glucoside* *The advantages of th injection method are* —

(1) *Certainty* of action, as all the drug gets into the tissues and therefore the dose i definite

(2) Rapidity of action, as the drug quickly reaches the circulation

(3) When *administration by the mouth is not possible as when the patient* cannot swallow (unconsciousness, drunkenness etc) or when the alimentary tract cannot tolerate or absorb drugs (uncontrollable vomiting and diarrhœa)

ntages

The disadvantages are —(1) Abscess may form at the site of injection if precautions are not taken (2) the drug may be injected by mistake into a vein with disastrous results (3) the drug may be injected into a nerve giving rise to excruciating pain or paralysis (*e g*, quinine) All these can be avoided if sufficient care is taken

Only the best instruments make possible a good technique and on the technique depends a good deal of the success of the therapy It is not essential to possess a record syringe' An all glass syringe may serve the purpose even better provided it is made of alkali free hard (resistance) glass The graduation and capacity of the syringe must be accurate Tips of all glass syringes break easily if not properly ground or if the s ze and taper is not such as to fit securely and tightly into a needle The size of the tip should not be too long (*i e*, not more than ½ inch for 2 and 5 ccm syringe and 17/32 inchs for 10 ccm syringes) Proper and secure joint can also be afforded by a properly designed "lock" to fit the commonly used standard needles Proper fitting of the tip of the syringe with the needle prevents tip breakage, leakage of solution and 'com ing off' of the needle Some simple tests may help in the choice of a good syringe *Draw up slowly some water and see that no air intervenes* between the piston and the fluid Free working of the piston should also be tested The opening of the tip of the syringe should be of the same inside diameter as that of the largest needle used with each size syringe The fitting between the barrel and the plunger should obviously be neither too loose nor too tight

Accuracy of graduation of the syringe can easily be checked up by a standard measure A fine black line at the base of the plunger facilitates reading and regulation of dose For testing the glass for free doses from alkalies the Standard *Phenolphtha* lein Test of the United States Government may be employed

(1) Sterility of Syringes

on
e

There is much doubt and misconception about the efficacy of different methods of sterilizing syringes The Committee of the Medical Research council in its memorandum entitled The Sterilization use and care of syringes" has given a comprehensive survey of measures to ensure sterility There are also sections on the choice of syringes and needles the care and sharpening of needles, the methods of testing syringes for leakage, the organization of a *clinic for mass inoculation and the precautions necessary* in employ ing syringes for certain special purposes such as tuberculin tests, the withdrawal of blood for anti toxin estimations, and mass intra-venous injections

The first injunction is that *syringes used for aspirating septic material, should never be used for injection of a sterile medicament* The neglect of this elementary precaution

Autoclaving

may cause terrible disasters. There should be sufficient number of syringes and separate ones for different jobs. It is urged that there is no known method which can be absolutely depended on to sterilize a syringe except autoclaving or exposing to a temperature of 160°C in a dry oven. This seems to sound the death knell of the record syringe, since cement at the glass-metal junction is liable to melt at these temperatures. In fact all glass syringes of a two piece type are advocated. The all glass syringe is easily cleaned and has no obscure crevices in which previous contents may lurk. The best thing is to have plenty of such syringes to encase them in glass tubes and to sterilize them by dry heat. It is advocated that in a large hospital a single department should have the care of all the syringes, cleaning, sterilizing and re-issuing them for use.

Boiling

Boiling is given as a second best alternative; it will not kill sporogenous bacteria unless sodium carbonate is added to the water; this however is not recommended as the resulting alkalinity of the syringe may affect the solution to be injected. The risk of infection by sporogenous bacteria, though remote, exists. For this reason the dry method is preferred to a wet one. The boil oil method was tested and found to be ineffective.

Use of alcohol

Chemical methods of sterilizing a syringe, such as with hypochlorites, phenols, chloro-phenols, etc., are ineffective and may damage the material to be injected. Besides this they do not penetrate the crevices in which bacteria may lodge. The only chemical disinfectant receiving even a qualified recommendation is 70 to 75 per cent V/V alcohol and this should be only confined to syringes employed for and by a single patient for the injection of insulin and adrenaline. Alcohol acts best in a concentration of 75 per cent by volume in water and scarcely at all when undiluted. It acts only on vegetative bacteria and has little power of penetration. It is a better disinfectant than most for skin but unreliable when absolute sterility is necessary as for instruments. It should also be remembered that when the skin is moist as in hot climates undiluted alcohol is effective and the concentration used should not be less than 80 per cent owing to dilution with sweat. Ether has been tried as a skin disinfectant and has been found to be ineffective.

Injection material

Regarding solution for injection care should be taken not to include any solid particles from ampoules or tiny masses of undissolved drugs, which when present should be filtered out before injection.

A cold compress at the site of injection or application of an elastic bandage above the injected part will be found useful when it is desired to reduce the rate of absorption.

When a syringe becomes jammed any of the following procedures may help. Boil in 25 per cent aqueous solution of glycerine and remove the plunger while still hot. Put nitric acid or ether around the head of the syringe tip and allow it to permeate in between barrel and plunger before they are separated. If it is a record syringe put it in the refrigerator for sufficient length of time and later draw out the plunger. Stains on the syringe can be removed by nitric acid.

Needles

A good needle should have a clean cutting edge, flexibility and strength. The needle point should have no irregularities. These can easily be detected by a hand lens, or by drawing the needle back across a piece of gauze or the finger nail. Needle points have varying types of bevels; the long bevel for aspiration, subcutaneous and intra-muscular use and the short bevel for going into the vein. Extra short bevel is recommended for intradermal and spinal use. Regarding the size of the needle, the depth of the tissue being aimed at, safety, rate of flow and lastly the question of pain to the patient should be borne in mind. Extended use weakens the needle and increases chances of breakage. Before sterilizing every needle should have its flexibility tested; this can be carried out by bending the shaft of the needle forwards and backwards. A steel needle three inches long should be able to make an arc of about 45° and spring back to normal, smaller needles would obviously make smaller arcs. For keeping needles free of rust etc., these should always after use be syringed out with water, alcohol and ether so that they remain dry.

(2) Subcutaneous or Hypodermic Route

Subcutaneous route

In this method the drug is given into the subcutaneous tissues by means of a hollow needle. All preparations meant for subcutaneous injection should be in liquid form, solutions or colloidal suspensions and should be capable of complete absorption, for otherwise they will set up irritation. The quantity injected should not be too large (under 5 ccm). Large quantities of saline are sometimes injected into the loose tissue about the

breast axilla abdomen or into the back below the scapulæ the liquid being allowed to run in slowly Care should be taken that the fluid is neutral in reaction and is isotonic or nearly so with blood for otherwise it will not be absorbed and pressure on vessels may *cause gangrene or abscess*

(3) Intradermal Route

Intradermal injections apart from a few therapeutic or prophylactic uses (*e g* small pox vaccination Besredka s antivirus leprosy and certain foreign proteins etc) are mainly employed for diagnostic purposes (*e g* Schick Dick and various allergic tests) The injections are given on the flexor aspect of the forearm generally and when the needle is *in the proper position the opening in the level should be visible through the* epidermis The quantity of the fluid injected is specified in the tests but does not exceed 0 2 ccm Details of some of the important tests are given in the dictionary

(4) Intramuscular Route

The injected substance ruptures the muscle bundles and spread along the nearest fascial planes thus greatly increasing the absorbing surface The absorption therefore is more rapid than with subcutaneous administration and *in view of the fact that sensory* nerve endings are fewer than in the skin there is less pain The tendency to abscess formation is also much less Intramuscular injections are particularly useful when relatively insoluble substances suspended in oil have to be administered These establish a depot for gradual absorption and continued action *e g* mercury salicylate in the treatment of syphilis. *Suspension of metallic salts in oil are best injected intramuscularly* as they are hardly absorbed from the subcutaneous tissues

Intramuscular injections are made by thrusting the needle through the skin deep into the substance of the selected muscle The buttocks are most commonly selected for these injections and the most favourable site is the upper and outer quadrant If the injected material is deposited near a nerve root nerve plexus or nerve trunk, obstinate neuritis may result and if deposited on the fascia of the region superficial nodule formation abscesses or deep firm indurations may develop The tissues at the selected site should be flattened and fixed with the palm of one hand and the needle inserted at the selected point The plunger should be withdrawn slightly to make sure that the point of the needle has not entered a blood vessel The injection is then given slowly With proper technique the flow of the injected material is always free and unobstructed Provided the needle points and syringes are mechanically perfect and the buttocks have not been rendered fibrous by repeated injections there should be no leakage along the needle track Excepting where the buttocks have been rendered fibrous the leakage may be prevented by securing complete relaxation of the musculature by the use of a small gauge needle by completely emptying the needle before rapid withdrawal by pushing upward of the tissues pulled down by the left hand and lastly by gentle massage at the point of puncture with a pledget of cotton wool saturated with alcohol When repeated courses of injections have rendered the buttocks fibrous leakage cannot be prevented and ultimately intramuscular injections must be discontinued in this region

It must be remembered that due to faulty technique worn out needle or want of co operation of the patient a needle may break inside the muscle This is usually due to ageing of the needle which is thus rendered brittle The usual break is at the junction of the shaft and the hub This complication is mostly prevented by the use of best makes of needles or the use of safety needles with bend on the shaft and in either case the needles should not be very old *As already stated persistent nodule formation* abscess formation and neuritis are other complications

(5) Intravenous Route

During recent years the practice of intraveous medication has come to the fore front Twenty years ago medical men would not willingly undertake the injection of a drug into a vein Now a days however the popularity of the methods has increased and the modern *physician performs* this operation with alacrity and skill Attempt is made to give almost every drug by this route on the assumption that intravenous medication produces a more powerful therapeutic effects than administration of drugs by other channels This misconception has assumed such proportions that it is both timely and important to
... his form of therapy
... s first started in 1655 when Christopher Wren
... gs could be given into a vein without ill effects
... on was given in man The discovery of sal
... the beginning of this century and its safe intravenous use put intravenous

therapy on a sound and stable basis (1910) The demonstration of the relative harmlessness of intravenous salvarsan injection came as a great relief to the physician who could thus treat syphilis without giving the patient the excruciating pain attending on intramuscular injections

Physiological considerations

A knowledge of the inherent properties of the blood is essential in order to have a closer conception of this method of administration A brief reference to the physiological considerations will not, therefore, be out of place here

The blood is the chief medium through which any drug introduced by any channel will be distributed to different parts of the body It is a special fluid, having the function of carrying nutrition and oxygen to all the tissues and eliminating the waste products that accumulate as a result of metabolism It also takes certain chemical substances that are formed by physiological activity of an organ to other organs thus regulating and
ody The total volume of blood has
dy weight The erythrocytes form
wo parts stroma and haemoglobin in
y be broken up by various means
of ether or bringing it into contact
with water makes the consideration
of the *osmotic relations of the erythrocytes* an *important study in intravenous injection* If the osmotic pressure of the blood plasma is reduced by diluting with water the corpuscles in order to maintain the balance break up liberating their haemoglobin If a strong solution of common salt is added to the blood so as to make the osmotic pressure of the plasma higher than that of the erythrocytes water will pass from the corpuscles

stances such as alcohol ether etc however can permeate through the corpuscles The blood corpuscles resemble most animal and vegetable cells in permitting the passage of those substances that are soluble in fat and fat like bodies *e g* lecithin and cholestrin

Specific gravity

x varies between 1056 and 1058 and in
cific gravity becomes important when
as in cases of cholera If the
in this disease very large quantities
When the specific gravity is within
saline is liable to produce œdema of
lungs and death.

Reaction of blood

The hydrogen ion concentration of the blood is another important consideration in intravenous therapy The blood as is well known is alkaline to litmus The pH of this fluid depends mainly upon the ratio between the concentration of carbon dioxide and bicarbonates in the blood, and these two are so balanced that the pH is just on the alkaline side of neutrality This balance may be expressed as an equation pH (hydrogen ion-concentration) $= K \frac{H_2CO_3}{NaHCO_3}$ where K is a constant An addition of a trace of acid or alkali will disturb the balance by increasing or decreasing its numerator or denominator and make the pH move towards the acid or alkaline side of neutrality The tissues and
of the blood at a constant level The mechanism by which the neutrality of the blood is maintained is described in detail in chapter on acidosis and alkalosis

The balance of pH is so delicately maintained that ordinary injection of drugs which are distinctly acid or alkaline produce no permanent change in the reaction of the blood. If, however, the rate of injection is rapid the buffers present may not be able to keep the balance intact.

Blood volume

The volume of the blood is another important subject for detailed study in connection with intravenous therapy It is a well known fact that the blood volume remains fairly constant despite influences which tend to alter it After a severe hemorrhage, the volume of the blood is made up by gradual imbibition of fluid from

the tissues Again when large quantities of saline solutions are injected into the circulation the total blood volume does not alter permanently However the effects produced immediately are dependent on the strength of the saline its temperature and on the speed with which it is driven in A hypertonic solution attracts fluid from the tissues brain and cerebrospinal fluid into the blood circulation but in case of hypotonic solut ons the reverse happens and some water is drawn out from the blood into the tissues brain and the subarachnoid space If the — . f l. d d -her than the body temperature a direct action on lar node is produced and the heart accelerates erature the heart is slowed Regarding the speed rapid the venous pressure is raised and as ultim arterial system blood pressure temporarily rises With slow injections no such change is produced In animals such as cats and rabbits about 100 to 200 ccm of normal saline infused slowly do not produce a rise in arterial pressure proportionate to the quantity injected The fluid therefore must be accommodated either inside or outside the vascular system There may be dilatat on of the arterioles and capillaries to make room for the extravolume of fluid or the fluid may pass out of the circulation into the tissues as lymph Both factors appear to operate simultaneously Immediately after such a transfusion an increased fullness in the vessels *of the mucous membrane and retina can be observed* The fluid portions of the blood however rapidly pass from the blood vessels to the tissues giving rise to œdema if the quantity of the fluid transfused is very large This œdema might set in in such vital organs as the lungs and may produce serious respiratory distress or even death

The question of the entry of air into the circulation may be briefly reviewed here It is a matter of common observation in laboratories that small quantities of air introduced into the circulation do not have any deleterious effect on an animal On the other hand injection of large quantities of air is the quickest and surest method of killing an animal 5 ccm of air suddenly introduced into the vein of a rabb t will produce fatal results within 2 or 3 minutes If however the air is introduced slowly the animal *does not die If 5 to 10 ccm of air are injected* abruptly into the vein of a cat an immediate fall in blood pressure to zero is produced The churning of blood and air in the heart produces froth and sudden heart failure may occur due to very small quantities of blood entering the coronary arteries with consequent impairment of the nutrition of the heart It must be realised, however that in order to produce such result in man the quantity of air introduced must be very large Five to 10 ccm of air ever *when introduced suddenly will be rapidly absorbed by* the blood and will produce no deleterious effects whatsoever

The select on of the salt to be given when several salts of an alkaloid are available should depend upon the solub lity of the salt and its rate of diffusibility Generally the hydrochlorides are more soluble and more diffusible than the sulphates because of the smaller size of their molecules Another point in favour of hydrochlorides is that HCl combines with the calcium of the blood forming calcium chloride which is soluble The calcium content of the blood will therefore not be affected If a sulphate is given the insoluble calcium sulphate wh ch is produced will be precipitated and will deprive the heart of its proper calcium requirements The chem cal changes such as those occurring in the blood however are so insignificant with ordinary injections that their effects are negligible in view of the large volume of the blood in circulat on

— - l f -mony produce a precipitate s but the symptoms pass such as salvarsan are not not hold them in complete e

The following are some of the chief ind cations for the administration of drugs by the intravenous route

of act on is desirable A few ex combating acidosis in the body *e g sodium bicarbonate* insul n etc may save the patie t s y intravenous injections of calcium may prevent death (*c*) In auricular fibrillation with impending death an intravenous injection of strophanthin may act like a charm (*d*) In malignant malaria intravenous admin stration of quinine or atebrin produces rapid curative effects (*e*) Severe cases of *diphtheria* generally demand the intravenous use of ant toxin and often respond favourably

2 When greater intensity of action is desired than can be secured by other methods of administration Arsenicals are given in syphilis by this route to produce an effective concentration in the blood Antitetanic, antimeningococcic and antistreptococcic sera (especially for scarlet fever) are sometimes given intravenously to produce stronger action than can be obtained when given subcutaneously Non specific proteins, when used to induce protein shock, are best given into the vein, *e g*, typhoid vaccine in chronic arthritis

3 To secure direct action on the infecting organisms within the blood stream *e g*, quinine in malignant malaria

4 To avoid irritation and destruction of tissue likely to be produced by drugs, such as arsenicals and antimonials, when given by other routes

5 When the volume of the fluid is large it is better to give it intravenously than intramuscularly or subcutaneously, *e g*, injections of saline in cholera Though large quantities of saline can be given under the breast and in the loose areolar tissues of the axilla, the procedure is very painful and should be avoided as far as possible The various advantages of intravenous therapy over other modes of administration are —

Advantages

1 Precision of dosage This can only be attained by injecting a drug straight into the blood stream. *There is no certainty what amount of a drug administered orally is going* to be absorbed finally into the circulation

2 Absence of gastro-intestinal irritation Some arsenicals and antimonials cannot be given by the mouth

3 Stability of the drug *e g*, adrenaline and many hormones are rendered inert when given by the oral route

4 Prompt action

5 Avoiding irritation or destruction of tissue when given by subcutaneous or intra muscular method

Disadvantages

Intravenous medication should not be resorted to if a drug can be effectively given by any of the other routes as there are many risks attached to this form of medication There is a growing tendency on the part of medical practitioners to resort to intravenous injections when the utility of this method is doubtful This is to be strongly deprecated The injection of foreign substances into the blood stream should always be considered a serious undertaking and the advantages and disadvantages should be carefully weighed before it is actually practised The risks of intravenous injection frequently outweigh its probable benefits in (a) greatly debilitated patients (b) the aged (c) patients with hypertension and arteriosclerosis, (d) patients suspected of being sub ject to anaphylactic reactions, *e g* [illegible] ther more, the injection of substances [illegible] deli cate physiological balance of the [illegible] acid or alkaline in reaction imperfectl [illegible] solve in water, hæmolytic agents emulsion [illegible] may be serious.

Technique

[illegible]

very prominently The disadvantages in using this vein are that the skin over it is usually tough and there is a nerve just under it which may be accidentally injured.

The veins on the innerside of the ankle or veins of the neck are some of the other alternatives. Varicose veins should not be used The skin over the vein should be sterilised with alcohol If iodine is used it must be washed off with alcohol, otherwise [illegible] the skin with xylol will increase [illegible] Engorgement is caused by putting [illegible] which the vein is to be punctured [illegible] al flow to the limb Further conges

tion may be caused by gentle upward massage or by rapid extensor and flexor movements of the limb by the patient In very nervous subjects local anaesthesia by ethylchloride spray or by injection of one drop of 2 per cent novocaine may be given if feasible before venipuncture is performed The patient should be either lying down or sitting at a table with the elbow on a small pillow The syringe should be held in the right hand at an angle of about fifteen degrees with the skin surface and entered upwards and along the long axis of the vein The point may enter the vein immediately or the vein may slip to one side in the latter case the point of the needle must be made to follow the vein pressing into the side of the vein until it is pierced The level of the needle should point upward and the mark on the syringe should be facing the operator Directly the vein is punctured blood will enter into the barrel of the syringe which has been previously loaded with the dose that is to be injected The congesting band is now released and the solution [illegible] possible [illegible] mum do [illegible] effort m [illegible] the oppo [illegible] home of [illegible] the patie [illegible] point is [illegible] drawing [illegible] the syringe Great care must be taken that no air escapes into the vein from the syringe

In children who are very likely to wriggle during the operation a good method is to hold the syringe in the right hand and with the left hand grip the arm so that the back of the elbow lies in the hollow of the hand and the first two fingers and the thumb can be approximated in front of the elbow as the needle is passed into the vein the barrel of the syringe is gripped between the fingers and thumb of the left hand so that the syringe and the arm cannot possibly move independently It will not be found necessary to grip so tightly that the venous flow is stopped

The drugs used must be of established purity determined by chemical or biological methods and should be freely soluble in ordinary solvents Substances which are imperfectly soluble should on no account be injected into the vein unless they are in a colloidal state

(*a*) The water used for the solution of the agent to be injected must always be double distilled sterile and free from pyrogens

(*b*) Sterility of the solution just before injection is essential This may be attained by autoclaving the solution if there is no chance of the drug breaking up by heat

(*c*) The possibility of decomposition of the solution should be borne in mind Heat converts a part of $NaHCO_3$ into a much more caustic and alkaline carbonate Such substances as strophanthin are decomposed when their solutions are put up in soft glass ampoules owing to the liberation of alkali from the glass The physician should see if hard glass has been used for such ampoules before giving the injection

(*d*) The reaction of the solution is important All solutions for intravenous use should conform as closely as possible to the reaction of the normal blood which is slightly on the alkaline side of neutrality (pH 7.4)

(*e*) Solutions should always be as nearly isotonic with the blood as possible whenever the volume of fluid to be injected is large Exception to this are conditions such as cholera and high intracranial pressure when hypertonic solutions are necessary

(*f*) The rate of injection of the solution should be slow in order that the circulation is not overwhelmed with large volumes of the fluid which it cannot cope with rapidly Injection at a slow rate is specially important in connection with potent drugs like arsenicals and antimonials

(*g*) The temperature of the solution should be approximately that of the body otherwise unpleasant reactions might result

There are various risks attendant on intravenous therapy and in order to avoid [illegible] themselves with the details of the [illegible] in the blood is maintained the [illegible] ise with which it may be upset and [illegible] Anaphylactoid phenomena evidenc[illegible] ay follow immediately after intravenous injection especially [illegible] ces such as saline or glucose are given Such reactions are very disturbing and their real nature is not clear It has been

shown that distilled water frequently contains a pyrogenous body which is the product of its contamination with living organisms This pyrogen is produced by the growth of the organisms and is not present in freshly distilled water The water used should therefore be freshly distilled unless it is properly preserved The other view is that the anaphylactic reactions are the result of physico-chemical disturbances in the plasma set up by rapid changes in the blood The temperature of the fluid at the time of its entrance into the vein is also important It should be realised that the temperature of the solution in the funnel or glass barrel used in the gravity method is not the same as that at the tip of the needle, for the solution cools down during its passage through the rubber tubing

No agent should be used for intravenous injection which has got any deleterious effect on the circulation and is therefore likely to produce dangerous reactions A dangerous cond t on from the ... le in large quantities has been describ ... 10 gm or more—a condition of ... in and increase in the total volume of ... gravity falls from 1064 to 1054 after an injection, the kidneys and lymph channels promptly excrete the excess of fluid and may overshoot the mark so that eventually the specific gravity may rise to 1067 the total blood is less in bulk and even more concentrated than it was before This does not occur if the supply of fluid is kept up by administering saline per rectum

Hydraemic plethora

If the kidneys are not capable of excreting water and salt quickly enough there will be water logging and some degree of dropsy may occur This may take the form of fatal œdema of the lungs This danger has frequently been met with following saline transfusion especially in patients with nephritis

Thrombosis and embolism have frequently been mentioned as the most dangerous outcome of intravenous therapy and numerous instances of death following thrombosis and embolism of the pulmonary capillaries have been recorded It is possible that sudden death might follo ... heart by blocking the coronary arte ... embolism are seldom met with in ... the solution in the syringe do ... hance of thrombosis starting at th ... irritant to cause damage to th ... dditional quantity of saline should be injected to wash down the irritant drug This is the usual practice with drugs like salvarsan

Thrombosis and embolism

There are other associated dangers not directly due to the injection but the results of fa lt ...

Leaking punctures

be prevented with proper care and attention on the part of medical practitioners

(6) Other Routes

In addition to the preceding main parenteral routes of drug administration there are a number of others which are resorted to occasionally A drug may require to be introduced directly into the subarachnoidal space and a lumber or a cistern puncture may have to be performed Spinal anaesthetics antimeningococcal serum tetanus antitoxin penicillin etc are the usual remedies which are given by this route

Subarachnoidal

In some extreme situations it may be advisable to inject such drugs as epinephrine direct into the heart An intracardiac injection is usually given in the fourth left intercostal space just inside the clinical apex beat using a needle about four inches long Before the injection the position of the needle in the ventricle should be ascertained by aspirating some blood.

Intracardiac

Intraperitoneal injections are on rare occasions resorted to when other routes of administration are not available The abdominal wall is entered in the middle line 1 2 inches below the umbilicus Before an intra peritoneal injection is attempted the urinary bladder must be emptied and the skin prepared in the usual manner A fold of skin is picked up at the selected spot and the needle is inserted into its lower part from below upwards In thin persons the passage into the peritoneal cavity can be felt After the needle is in the correct position it may with advantage be fixed to the abdominal wall by adhesive plaster

Intra peritoneal

may be defined as the prevention or treatment of disease by chemical disinfection or inhibition of the parasitic causes without marked or serious toxic effects" It is that branch of the science of biochemistry which deals with the therapeutic properties of certain chemicals in the curative and prophylactic treatment of parasitic diseases

The chemical agent may be natural or synthetic Thus quinine is as much a chemo therapeutic agent as arsphenamine Location of the parasite does not affect the definition in any way The parasite may be in the blood in the lymph ... tissues or on the external surface (skin and muco ... therapy in the modern sense includes the treatment ... ment of hookworm by carbon tetrachloride the ... s with sulphonamide derivatives or the treatment ... essential factor is the complete routing or crippling of the parasites no matter what their nature and location may be without seriously damaging the cells of the body

2. Theories of Parasitotropism and Organotropism

(1) Side-Chain Theory

Ehrlich applied the same theory to explain parasitotropism and organotropism as he did to explain the theory of immunity Kolmer gives the following extract from Ehrlich's Harben lectures

I also wish to lay special stress upon my view that the drugs are attracted by and bound to the protoplasm molecule by certain atom groups I am inclined to look upon this as somewhat analogous to the binding of the toxins and of similar protein bodies Yet on the other hand there are fundamental differences between the two For as I have always insisted the mode of binding the toxins is peculiar in so far as it is the result of a certain kind of assimilation which obviously consists in a process of a more or less synthetic nature. These toxin receptors which produce immunity are bodies of a more independent character and appear to be especially destined for purposes of assimilation This high degree of independence is evidenced by the fact that in conformity with my side-chain theory these receptors are very easily reproduced by the cell in excessive numbers and after being separated from the cell find their way into the blood

I have now formed the opinion that in like manner a part of the chemically defined substance is attached to the cell by groups corresponding to these receptacles these atom groupings I will distinguish from the toxin receptors by the name of chemo receptors This view is more practically supported by the fact that an atoxyl fast strain of trypanosomes is also resistant to a number of substances related to atoxyl but otherwise showing widely different chemical characteristics Evidently therefore the arsenic acid radical here represents the point of attack which is common to this series of substances There chemo receptors must however be regarded as of a simpler structure than the toxin receptors They do not show a similar degree of independence, nor can they be thrown off into the blood The number of such chemo receptors for poisons which trypanosomes possess represents the number of points of attack. By means of the resistant strains we can count off one by one these groups that are open to attack.

This theory ex... drug for a parasite or a cell by supposing that ... to which these compounds become attached ... ous dyes and arsenicals on infective organism ... lent strong support to his hypothesis According to him a chemical agent cannot exert its action on the parasites unless fixed by suitable chemo receptors of the cells of the parasites When arsenic or any other drug is administered they are presumed to carry certain side arms which are anchored to the special receptors of the cells of the organism These side arms have greater affinity for the receptors of the cells of the parasites than those of the tissues of the host thus having a parasitotropic action with the least organotropic effect

(2) Chemical Theory

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of arsenic are spec fic po sons for the SH group of glutath one and poss bly other SH compounds in the protoplasm of the cell with a consequent suppress on of v tal funct ons h ch may expla n the toxic and therapeut c effects of organ c arsenicals l ke arsphenam n

3 Factors Influencing the Action of Drugs

Attent on has already been drawn to the d fferent results obta ned from *in vitro* and *in vivo* exper ments There is therefore some profound change occurr ng n the body wh ch g ves th s d vergence in the *in vitro* and *in vivo* exper ments The changes will ma nly depend on the channels of *absorpt on, for a var ety of* chem cal and phys co chem cal actions take place before the dr g s d str buted through the body to act on the paras tes t is meant to destroy

After oral adm nistrat on hydrolys s emuls ficat on sapon ficat on, etc occur n the gastro-intest nal tract before the drug s absorbed nto the c rculat on After absorpt on the detox cat ng propert es of the nternal organs especially the l ver play an mportant part in the mod ficat on of the drug The changes that occur after an intra enous nject on are also important for as the drug s d rectly introduced into the c rculation phenomena of lys s agglut nat on prec p tat on f prote ns etc may occur Important changes of ox dat on and reduct on may occur a d a ne v compound may be evolved after comb nat on v th certain cellular const tuents n the body

After absorpt on the chem cal agent s d str buted n the body not un formly but

agent to the t ssues

Acqu red or natural tolerance to the act on of drugs s a well known phenomenon Certa n ind v duals have got the power of tolerat ng large doses of po sonous drugs w thout sho v ng tox c effects In the case of hab t form ng drugs *e g* alcohol coca ne n cot ne e c the tolerance s probably psych c developed as a result of the nervous system gett ng adapted to continued se Other cases may be due to ncreased destruct on of the po son as s found w th op um and its alkal ds or the result of d m n shed absorption or increased el m nat on Another consp cuous nstance of tolerance s found in the format on of ant toxin Such ant tox n format on s the result of repeated adm n strat on of fore gn prote ns e ther an mal or bacter al Ant tox n format on has also been observed w th certa n glucosides snake venom po son vy etc

4 Drug Resistance

(1) General Features

It was n t however known t ll recent years that paras tes too acqu re tolerance to drugs This tolerance n paras tes to w thstand the de truct e ac on of a chem cal agent is known as *drug fa tness* A ast amount of l erature has s nce been p led up regard ng the nature of drug fa tness n ar o ra c nfect ons such as trypanosom as s sp rochaetos s and from th s s andpo nt the treatment of nfect ous d seases is of great nterest n order to dec de whether a part cular remedy does or does not produce res stance n the causat e organ sm Franke and Roehl working n Ehrlichs laboratory recorded interest ng observations on the drug fastness of trypanosomes Work ng w th nagana nfected m ce they found that aft r feed ng the m ce w h parafuchs n the paras te d sappeared from the per pheral blood After somet me they reappeared, and by cont nu ng the feed ng t was observed that success e adm n strat on of the dye became less effective n remo ing the para tes from the per pheral c rculat on Then a time was reached when the per d o ban shment of the paras tes fr m the c rculat on became pro gress ely shorter unt l the drug ent rely fa led to r d the blood of the organ sm After transference of the stra n to a healthy mouse it was found to be un nfluenced by the act n of parafuchs n The drug had therefore produced n the organ sm a he ghtened res stance to w th tand the otherw se fatal concentra o s of the same drug Th s nterest ng d scovery was soon followed by the further ob er at on that trypanosomes could devel p ow known that nearly all the drugs wh ch

possess equal potentialities of making trypanosomes resistant to their action In case of the aromatic arsenicals the drug resistance produced is not related to the arsenic *content* of the particular compound From the data collected by various workers some generalisations have been worked out Firstly it is held that a strain resistant to *an* aromatic arsenical *or antimonial compound is also* resistant to other aromatic antimonials or arsenicals But the degree of resistance set up may not be the same quantitatively in each instance Secondly, a strain resistant to aromatic *arsenicals is sensitive to tartar* emetic, but a strain resistant to aromatic antimonials remains resistant to aromatic aresenicals also

The phenomenon of drug resistance has been observed by various workers both in experimental studies and clinically in the treatment of bacterial *diseases* The *nature of* this resistance is only imperfectly understood but it is one of the most complex biological phenomena that has been observed in the reaction of the living organisms to the action of chemicals

(2) The nature and mechanism of drug-resistance

It is very difficult to say at present why and how a certain strain of organism acquires the character of withstanding otherwise lethal doses of a poisonous drug This resistance may be a character of the causative organism or it may reside in the tissues of the host. The idea that the resistance to the action of a drug is not a character of the infective *organism but of the invaded host has* been formulated Such a theory is not tenable as it has been established that a strain of trypanosomes in mice made resistant to an aromatic arsenical compound is similarly resistant when transferred to rats or rabbits and *vice versa*

The question now arises as to what this peculiarity can be attributed

Voegtlin has devised a theory which postulates that trypanosomes acquire resistance to arsenic by virtue of the development of an excess of sulphhydryl compounds which enable them to detoxicate the poisonous effect of arsenic. Kolmer also supports a similar theory and explains the phenomenon on the basis of a chemical interaction between the *drug and the parasite He believes that natural tolerance is* due *to* the absence in the protoplasm of the cell of the parasite of a chemical constituent capable of interaction with the drug administered, or the presence of a substance which unites with the drug and renders it inert Such a theory has, however, been criticised by Yorke (1931) who has shown that contrary to the hypothesis of Voegtlin the arsenic resistant trypanosomes do *not absorb any aromatic arsenicals even though these may be present in* concentration rapidly fatal to the normal strain of parasites

Some workers have recently adduced evidence which goes to support *the view* that resistant trypanosomes do not absorb the drug concerned Similar observations have been *recorded in* the case of *Treponema recurrentis,* though the normal spirochaetes did take up gold and arsenic from solganal and neoarsphenamine respectively yet resistant forms [illegible] of the drugs It is believed that the phenomenon may be explained [illegible] arious micro organisms *to changed environments* [illegible] radual dying out of the more sensitive individuals [illegible] s

Summing up the evidence by different workers it becomes clear that the exact mechanism of development of drug resistance is still to be *explained It is quite probable* that this phenomenon may ultimately be proved to be due to mutations in populations exposed to intensive selection over many generations Whether these mutations are a spontaneous occurrence or a result of environmental factors also needs exploration

(3) *Drug resistance in trypanosomiasis, lieshmaniasis, Spirochaetosis, amoebiasis, malaria and bacteria*

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In human trypanosomiasis the occurrence of drug resistance is a well recognised interesting clinical observation This phenomenon is more common in insufficiently treated patients who are given suboptimal doses of the *drug* concerned, thus affording chance to the trypanosomes to develop resistance against the drug This drug resistance is said to persist indefinitely in case of [illegible] ted th t resistance of trypanosomes against ar [illegible] *once* developed persists permanen [illegible] the resistant trypanosomes have [illegible] letely during the course of about f [illegible] pano *somes is the fact* that there [illegible] tance even survives a passage through the insect host of tryj [illegible] *ases*

important public health issues as there is no doubt that insufficient dosage of aromatic arsenicals has produced quite a number of drug resistant strains of trypanosomes These when taken by the Glossina and injected into another person would prejudice his chances of a cure as the particular strain received by this individual would react poorly to arsenical therapy

Experimental data regarding drug resistance on the part of *Leishmania donovani* is meagre Clinical observation however seems to justify the dogma that Kala azar patients can be sharply divided into two categories on the basis of their response to treatment with pentavalent antimonials A very large majority of patients fall into the class of ordinary cases whereas the rest turn out to be resistants A resistant patient has been defined as "one in which a cure is not effected by an ordinary course of treatment which will cure from 90 to 95 per cent of ordinary patients More often than not these resistant patients can ultimately be cured by means of repeated intensive courses of the usual treatment In most instances the drug resistance is only relative rather than absolute

The existence of drug resistant groups of spirochaets is not a very rare occurrence In case of *Treponema pallidum T recurrentis T anserinum* and others, drug resistance has been developed experimentally *T pallidum* becomes resistant to arsenicals relatively more easily than to bismuth or mercury compounds The exact mechanism of the development of this resistance has not yet been finally elucidated Instances have been recorded where syphilitics resistant to treatment had transmitted this feature along with their infection On the other hand in cases of marital syphilis instances are on record where one partner only was resistant to treatment the other responding normally Conclusion appears to be that drug resistance in syphilis may either be a result of some change on the part of *T pallidum* or due to some subjective peculiarity of the patient

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non alkaloidal amoebicidal remedies

Resistant cases of malaria have also been described by several workers Inability to *prevent relapses in many cases of plasmodium infection* has been ascribed by many to the resistance of the parasites to quinine

Though quinine resistant parasites may occur the possibility of the development of this character in practical therapeutics seems to be small Evidence available does not at present warrant the view that the failure of quinine treatment in some cases is due to the occurrence of quinine resistant parasites The mode and virulence of infection, the degree of susceptibility of the individual the species and the geographical race of the parasites, are also to be taken into consideration in the alleged cases of failure with quinine. *Faulty methods* of administration and inadequate dosage may be responsible for many of the cases of failure In addition non absorption of the alkaloid from the gastro *intestinal tract* has also to be considered before the existence of quinine resistant parasites can be proved

Drug resistance is also said to be encountered among bacterial organisms It has not infrequently been met with sulphonamide drugs and even with antibiotics such as penicillin Streptomycin

5. The Reticulo-endothelial System

(1) Introduction and general

In recent years the reticulo-endothelial system has attracted a great deal of attention from workers interested in different branches of medical science. The anatomist the physiologist the pathologist the hæmatologist and the immunologist have all evinced great interest in the study of this system and in the solution of one or more of its innumerable problems The pharmacologist who is interested in obtaining a knowledge of the mechanism of action of drugs has also been directing his attention to this system in the hope that a study of it might be helpful in furnishing answers to

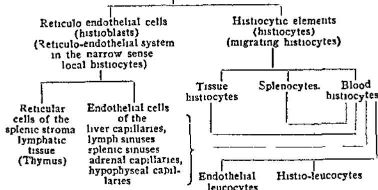
some of his problems A perusal of the literature on the subject reveals that the efficacy of many drugs, including some of the so called specific ones, may depend upon *the functional* efficiency of this system The earlier view expressed by Ehrlich and others that the chemotherapeutic action of drugs depended entirely on their direct action on the causative agent of disease, has now few supporters The accumulating evidence appears to be distinctly in favour of the view that drugs, in the majority of instances, act in an indirect way through the tissues of the body, and particularly through the cells of the reticulo-endothelial system Time and further work alone can determine the exact role of this system in infection, immunity and chemotherapy Incomplete though the knowledge may be at the present time, there seems to be very little doubt that the reticulo endothelial system plays a part of great importance in recovery from diseases more specially from those such as typhoid fever, tuberculosis, spirochætal infections malaria kala azar and trypanosomiasis In view of its increasing importance in tropical diseases it seems necessary to give a brief description of the system, its accepted functions in health and the part it plays in the cure of disease

Widely scattered in the blood and tissues of man and other vertebrates, there are *certain cells of mesenchymal origin and of the macrophage or large mono nuclear type* that possess the primitive capacity for phagocytosis and intracellular digestion These take up all foreign particles that gain access to the body, whether they be inert or colloidal inanimate or animate, bacterial or protozoal, and dispose of them in a manner best suited *to the body economy They collectively go by the name of the 'reticulo-endothelial system'*

The evolution of the reticulo endothelial system is closely associated with the origin and development of parasitism and host parasite adjustments 'In the long course of evolution of living things it seems probable that the lower forms of life arose far in advance of the more highly differentiated forms From the very moment of their first appearance upon this earth the latter had to compete for their place in nature with a vast number of microbial forms In the course of the adjustments necessitated by this complex communal existence various forms of parasitism were established In many instances invasion of a host by a parasite was fraught with danger, and as a defence against it mechanisms of protection of different degrees of efficiency were developed Even in the most primitive forms of life one or more simple means of self defence are discernable, as the needs for self-preservation become greater the mechanism of defence also becomes more complex" (W W C Topley) In the unicellular animal the function of protection is performed by the cell itself and is merely an adaptation of the ordinary feeding mechanism In lowly organised metazoa this function is relegated to certain special cells *In higher vertebrates and in man these cells of protection are very highly differentiated* and are distributed widely throughout the body, and go by the name of the reticulo endothelial system

The history of the recognition of the cells of the reticulo endothelial system may be said to have begun about the end of the nineteenth century Mallory's 'endothelial leucocytes' and Metschnikoff's 'macrophage cells' are now recognised to be reticulo endothelial cells and these workers, therefore, may well claim to be the first to recognise and point out *the importance of these cells Several subsequent workers also met with these cells* under various circumstances and referred to them under different names In 1913 Aschoff and Landau proposed to group together these differently named cells into a single system and to call it 'the reticulo endothelial system' In 1924, Aschoff gave a detailed description of the anatomical distribution of the cells composing the system and pointed out their functional unity and stressed their immunological importance

The reticulo-endothelial cells have a very wide and scattered distribution throughout the body They are to be found in organs such as the spleen, liver, lymphoid tissue bone marrow, connective tissue, blood and endocrine glands Amongst these organs, the spleen may be considered the largest store house of these cells The amount stored in the spleen as compared with other organs varies not only in different species of animals but also in different members of *the same species It has been found that after the* removal of the spleen regeneration of the reticulo endothelial cells takes place more quickly and markedly in certain species of animals than in others This has led to the presumption that the a [illegible] the spleen is also very variable and *dependent* [illegible] clearness, the anatomical distribution of the cel[illegible] classified by Aschoff is given below in a tabular form



Originally Aschoff classified the cell elements of the reticulo endothelial system into six groups according to the intensity of vital staining and the size and compactness of the dye granules present in their cytoplasm These groups are —

(*a*) The *endothelial cells* of the blood and lymph vessels

(*b*) The *fibrocytes* or ordinary connective tissue cells

(*c*) The *reticulum cells* of the splenic pulp and lymphoid tissue

(*d*) The blood *monocytes* and *splenocytes* [related to group (*e*) and (*f*)]

(*e*) The *reticulo-endothelial cells* lining the sinuses of the spleen bone marrow adrenal cortex and hypophysis

(*f*) The *histiocytes* or the large phagocytic motile cells of the connective tissue

Of these six types the first and the second are the least phagocytic, the third and the fourth moderately phagocytic, and the fifth and sixth the most phagocytic

The cells of the reticulo-endothelial system have been classified by Sabin into two main groups namely 'monocytes' and clasmatocytes The term 'histiocytes is preferable to clasmatocytes Under normal conditions these two types of cells are found in all organs containing reticulo endothelial cells The ratio of monocytes to histiocytes in spleen puncture material is generally 6 to 1 In the peripheral blood histiocytes are normally absent and the only representative of the reticulo endothelial system is the monocyte In pathological states and after experimental stimulation histiocytes as well as all grades of intermediate forms have been found in the peripheral blood These intermediate forms probably represent stimulated monocytes with increased phagocytic power The reticulo endothelial system has come to be recognised now as composed of two closely allied cell types These cells differ in morphology and possibly in function The histiocytes are said to play the chief role in the phagocytic mechanism of defence while the monocytes are more closely associated with antibody production

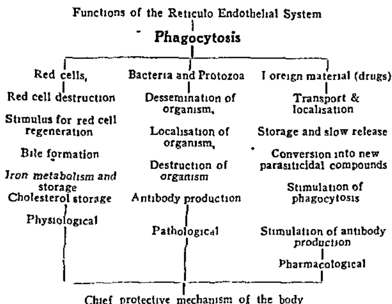
Normally the two chief cell types composing the reticulo-endothelial system as seen in supra vital preparations are quite distinct morphologically and can readily be distinguished from one another Typical specimens of the two types may be seen in the blood of malarial cases twenty four hours after an injection of quinine or in the spleen juice [illegible] treatment In these experimental and pathological [illegible] in classifying some of the forms intermediate [illegible] h a little experience and discretion this difficulty [illegible] are some of the characteristics of the two cell

Monocyte is slightly larger than the lymphocyte, which it closely resembles It has a big kidney shaped nucleus with a deep and distinct indentation or hof and shows the presence of a rosette or clump of uniformly fine neutral red particles at the 'hof and a number of blue-staining mitochondria in its cytoplasm Histiocyte is a much larger cell than the monocyte, its nucleus is very variable in shape and differs from that of the monocyte by being small in comparison to the size of the cell, by being often oval rather

than kidney shaped and by occupying a more or less central rather than an eccentric position The protoplasm of the histiocyte is somewhat granular, and mitochondria are generally absent, although occasionally, a cell may be seen with a few of them

Functions of the Reticulo-endothelial System

The reticulo-endothelial system performs a multiplicity of important functions both in health and in disease We already stated that phagocytosis is the chief characteristic of the cells of this system and to it we may add that it is this property that helps it to perform almost all its functions The best way to understand how that is done will be by tracing the sequence of events as they take place after phagocytosis of different materials The substances that these cells are known to ingest may be divided broadly into three main groups namely (a) red cells (b) organisms such as bacteria and protozoa and (c) foreign materials such as drugs For the sake of clearness the results of phagocytosis of these substances have been classified in a tabular form and then discussed separately in detail



Phagocytosis

It is an accepted fact that the cells of the reticulo endothelial system take up for purposes of destruction those red cells whose allotted span of life is over and also those that get damaged by inflammatory processes toxins or parasites In such diseases as malaria kala azar typhoid fever, Weil s disease and poisoning by arseniuretted hydrogen in birds and phenyl hydrazine in dogs phagocytosis of the damaged red cells can easily be observed When hæmoglobin is injected into the circulation it is also taken up by these cells *In vitro*, in tissue culture the histiocytes have been observed to ingest red cells Thus all observations made so far go to show that the histiocytes pick up old damaged or dead red cells in order to destroy them There appears to be no evidence however, to suggest that they phagocytose healthy and young red cells

Under normal conditions red cell destruction and regeneration are in a state of equilibrium and this helps to maintain the red cell count at a constant level The organ that is chiefly responsible for the control of the equilibrium appears to be the reticulo endothelial system The stimulus for red cell production is probably furnished by the histiocytic elements after they have ingested and digested the red cells It has been shown that when there is functional failure of histiocytes blood destruction is not followed by regeneration to any appreciable extent It is therefore probable that the reticulo-endothelial system provides the stimulus for regeneration of red cells and that in the absence of such stimulus the bone marrow fails to produce a sufficient number of red cells to make up the loss sustained

McNee (1913) suggested that the reticulo endothelial system as a whole is responsible for bile formation Subsequent workers clearly established, by extirpation of the liver and other experiments, that bile pigment is formed in all tissues in which reticulo-endothelial cells are present, including Kupffer's cells in the liver, but not by the glandular cells of that organ

One of the products of digestion of red cells and hæmoglobin is iron There is increasing evidence to show that the reticulo-endothelial system is concerned in the meta-

is of importance in the storage and metabolism of this metal

(2) Phagocytosis of Parasitic Organisms

Bacteria

It was shown long ago that bacteria injected intravenously are taken up largely by the endothelial cells of the spleen to the liver and the lungs There is also proof of phagocytosis of organisms in many infectious diseases Everyone is familiar with the persence of different bacterial organisms within macrophage cells in films of inflammatory exudates In infections diseases such as pneumonia, typhoid fever bacillary dysentery, tuberculosis leprosy, actinomycosis and spirochætal diseases the reticulo endothelial cells may actually be seen loaded with these organisms in infected tissues In all these diseases and in the granulomatous diseases, in particular, the characteristic cellular reaction is a proliferation and multiplication of the reticulo endothelial cells and the tubercle the leproma and the gumma are all formed as a result of this specific cellular immunity reaction.

Protozoa

There is considerable evidence to show that the blood inhabiting protozoa are also phagocytosed by the cells of the reticulo-endothelial system macrophage cells take up malarial parasites in birds red cells and malarial parasites have been found within the large mononuclear cells Despite this, there are some who still believe that the cells of the reticulo endothelial system take up only dead or dying malarial parasites Recent observations in connection with the role of the reticulo-endothelial system in malaria have shown that the cells of the reticulo-endothelial system phagocytose living as well as dead malarial parasites In kala azar oriental sore and dermal leishmaniasis Leishmania are mostly found with
perimentally when L. donovani ar
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they are picked up by the cells of
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of phagocytosing many of the blood inhabiting protozoa.

There is no evidence that the cells of the reticulo-endothelial system phagocytose helminthic worms that gain access to the blood or tissue It is probable that they take up antigenic substances liberated from the worms, either during their life or after their death and disintegration and lead to the production of antibody What part this antibody plays in overcoming the helminthic infection it is not possible to say and as such the role of the reticulo-endothelial system in diseases due to worms still remains a mystery

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to show that some of the organisms survive and even multiply within these cells In the case of leishmania and hepatozoon infections, the parasites actually live and multiply within the reticulo-endothelial cells It has been shown that certain *bacterial organisms* are found alive within phagocytes and that the latter at times afford the bacteria protection from the injurious effects of serum antibodies in their environment It is clear that phagocytosis and destruction are two separate functions of the cell and need not necessarily be present together at one and the same time Depending upon the functional state of the cell, the nature of the organism ingested, and certain other factors, death may or may not occur after phagocytosis It has been shown that one of the factors that helps to destroy parasites effectively is specific antibody Although the importance and value of antibodies in different infectious diseases vary, being probably high in virus and certain bacterial infections, moderate in protozoal infections, and slight in helminthic infections, there is evidence that antibodies do sensitise all parasites in such a way that other destructive processes, such as phagocytosis and lysis, can carry on their functions more successfully

The site of formation of antibodies has been a disputed question for a considerable time Years ago Metchnikoff suggested that the macrophages secrete some kind of ferment which helps them to destroy the parasites they ingest Later, this view was given up, and the belief arose that antibody was elaborated by all tissues locally, at the site of inoculation of antigen Recently, a large number of investigators studied this question and their work strongly indicates that formation of antibody takes place only in the reticulo endothelial system Splenectomy experiments are all in favour of this view The most suggestive evidence, however, in this connection has been obtained by tissue culture work It is evident that an antigenic substance irrespective of its source or nature introduced into the animal tissue is taken up by the cells of the reticulo endothelial system and removed to organs, such as the spleen and liver, where they stimulate the production of suitable antibody Antibacterial, antitoxic and lytic antibody are all formed according to requirements

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The chief characteristic of the reticulo-endothelial system that led to its discovery is phagocytosis of foreign substances There is an enormous amount of evidence to show that its cells readily ingest substances such as vital dyes carbon and Indian ink particles If, for instance, one of these substances is injected intravenously into a rabbit and then films from spleen, liver and lung are examined particles of the injected substances can be detected within the reticulo endothelial cells While little difficulty is experienced in demonstrating the presence of inert and coloured particles such as those mentioned above the detection of soluble chemical substances (drugs) that are generally used in the treatment of disease is a difficult matter By the use of microchemical tests and special staining methods, colloidal and organic preparations of metals, such as iron, silver antimony, bismuth and arsenic have been shown to be present within the reticulo endothelial cells As regards the finding of alkaloidal and other drugs *e g*, quinine within these cells there is very little evidence, it is possible that they are also taken up by these cells and removed to the spleen, bone marrow, suprarenals and kidney

Regarding the disposal of particular substances after phagocytosis, there is evidence that the reticulo-endothelial cells in the course of their wandering transport them to various organs and tissues (lung liver, spleen bone marrow and kidney), where they are either eliminated or stored Very little is known about the fate of soluble chemical substances probably a considerable quantity is excreted within a short time through the normal channels of elimination and only a very small quantity is found in the body, possibly in the reticulo endothelial cells Here they are present either in their original state or in an altered form As most of these foreign substances gain access to the body as drugs at a time when it is in a diseased state, the question of prime importance is how they bring about cure and beneficial results and what part the reticulo endothelial system plays in it

(3) Relation to Chemotherapy

It is unfortunate that despite a large amount of experimental work very little progress has been made in the understanding of the mode of action of drugs in diseased states or of the role of the reticulo-endothelial system in pharmacotherapy In the case of protozoal infections we possess knowledge about the specific action of some drugs Being of far bigger size than bacteria and more easily demonstrable in the blood and tissues by direct examination of smears we can get a true picture of the effect of treatment on protozoa and on the course of infection, and we can also correlate these findings with various cytological and serological changes This has enabled workers to tackle several

of the problems in chemotherapy through investigations on protozoal infections, such as

simple direct action on the parasites It may be true that in certain helminthic diseases and possibly also in some protozoal infections the action of specific drugs is predominantly
of other remedies there is absolutely no evi
effect It has repeatedly been shown that
gs when they are brought into contact with
rmore, drugs are rapidly excreted from
ccur in the blood and tissues after their
administration in therapeutic doses is so very high that simple direct action alone can hardly be said to account for their efficiency Blockade and splenectomy experiments have clearly established that dysfunction of the reticulo endothelial system reduces and at times completely abolishes the therapeutic value of drugs In view of these and other observations the consensus of opinion is that the reticulo endothelial system plays an important part in chemotherapy

It would appear that in bringing about cure the direct action of drugs on parasites is of the greatest importance in helminthic infestations of moderate importance in protozoal and bacterial infections, and of least importance in most of the virus diseases As regards the importance of the reticulo-endothelial system in overcoming infections, the reverse order appears to be the most likely i e the system plays a part of slight importance in helminthic diseases of moderate importance in protozoal and bacterial diseases of the highest importance in virus diseases How far these views are correct time alone can decide

Mode of action.

The different ways in which the reticulo-endothelial system can possibly help drugs in bringing about a cure are —(1) That it acts as a store house for the drug and releases it slowly as required—thereby preventing rapid elimination and ensuring continuous supply (2) That it carries the drug to the neighbourhood of lesions, where it is most needed (3) That it elaborates new compounds from the drug with greater parasiticidal power (4) That it is stimulated by the presence of the drug in circulation and thereby its functions of phagocytosis and antibody production become more pronounced and effective In support of the above view the following evidence may be cited It has been shown that when germanin (Bay
on account of
'second spleen'
into monkeys
was also a concentration of infection with *Leishmania* It has also been experimentally shown that the reticulo-endothelial cells localise certain colloidal substances, especially those that carry a negative electric charge in inflamed tissue in preference to other tissues This establishes the second contention A study of the action of arsenic compounds in splenectomised and nonsplenectomised animals suggests that the reticulo-endothelial system is probably concerned in the conversion of these compounds into more efficient germicidal substances This corroborates the third contention

The phagocytic function of the cells of the reticulo endothelial system is stimulated by quinine in malaria and this is said to be partly responsible for the cure of the disease The antibody formation is said to be increased after antimony treatment of kala azar and that this probably is responsible for cure These observations lend support to the fourth contention

Further evidences in support of the above can be obtained from a discussion of the mode of action of some of the important drugs used in the treatment of different infectious diseases The following is a brief reference to some of them —

Role in helminthic infections

The role of the reticulo endothelial system in the chemotherapy of anthelmintic drugs is not fully understood Although the evidence is strongly in favour of the mode of action of these drugs being a direct one on the worms themselves, there are suggestions in certain cases, that the beneficial results obtained may be attributable in part at least to an indirect action which is dependent upon the functional efficiency of the reticulo endothelial system This view appears to be supported partly at least by the results of treatment of helminthic infections of the blood and tissues The dermal tests reported to be useful in the diagnosis of some helminthic infections such as schistosomiasis, hydatid disease trichiniasis, filariasis and intestinal worms are evidence of sensitisation to antigenic substances from the worms, and are most likely due to sessile antibodies

elaborated by the reticulo endothelial system If it is so then the system may be presumed to play some part in the cure of these infections But at present we are not in a position to understand what exactly is the role of these antibodies in helminthic diseases

The role of the reticulo-endothelial system in the treatment of protozoal infections has been extensively studied Although there are several drugs which may be called specifics and which are known to act indirctly through the reticulo-endothelial system the mode of action of a few of the more important ones alone is discussed below

While there is evidence to show that the therapeutic efficiency of this drug in human amœbiasis is probably due to a direct action of the alkaloid upon *E histolyt a* the work of Dale and Dobell clearly suggests 'that emetine and the amœba are not only factors to be considered in the cure of *dysentery and that the missing factor is probably* the interaction between emetine and the host s tissues If this is correct then what other tissue of the host can play this important part more successfully than the ubiquitous reticulo endothelial system? Available evidence does not suggest the way in which the *system enhances or ensures the efficiency of the drug*

The mode of action of quinine in malaria has been studied by different workers but the views regarding it are still very varied. While some believe that the drug attacks the parasites directly others claim that it acts in an indirect manner through the host's tissues It has been shown that quinine by accelerating the natural processes of mobilisa tion proliferation and functional activation of phagocytic large mononuclear cells, brings about rapid engulfment and ult mate destruction of the malarial parasites Whenever the drug fails to elicit the suitable reticulo endothelial response no improvement is noticeable and after splenectomy of monkeys infected with *P knowlesi* quinine fails to bring about *the same degree of beneficial results* as when the organ is present. *It has been recently* (1944) shown by congo red intra venous injection method that quinine in therapeut c doses increases the efficiency of the reticulo-endothelial system and in unchecked malaria this system is depressed When malaria infection is duly checked by quinine it is stimulated *These results leave no doubt that the reticulo-endothelial system plays a part in the* cure of malaria by quinine

The mechanism by which antimony destroys *Leishmania donovani* and brings about cure of kala azar is still unknown It is very doubtful that it is a direct parasiticidal action *It has been shown that tartar emetic has no action on Leishmania donovani cultures in* [illegible] riantly in NNN tubes to which neosti [illegible] NN tubes When antimony compounds [illegible] ly in the urine the d lution in which [illegible] s stay in the circulation is not very [illegible] ossibly be conceived of in such low [illegible] the tissues of the body is therefore [illegible] and Chopra and Das Gupta (1929) [illegible] intravenously into kala azar patients it causes enlargement and rhythmic contractions *of the liver and spleen and that this is* due to an increased functional activity of the adrenals This observation led them to suggest that the alteration in the permeabil ty of the vascular walls brought about by the hyper activity of the adrenals caused a diminution in the permeability of the cells of the reticulo-endothelial system and this in turn led to the starvation and death of the leishmania parasites present in them These findings have been confirmed in an indirect manner by studying the changes in the leucocyte picture after adrenalin inject on into kala azar cases before during and after treatment. This work clearly indicated that a condition of hypoadren a existed in kala azar cases and that treatment helped to bring about a normal condition. But what part this alteration in the *adrenal n content played* in overcoming the infection could not be clearly determined Certain cytological studies on *kala azar patients with the help of supravital staining technique showed the importance* of the reticulo endothelial system in infection and immunity in kala azar It was found that within *the animal body Leishmania donovani* are present only within histiocytes and that in untreated kala azar cases there is an enormous increase in the hist ocytic elements of the reticulo endothelial system and a reversal of the normal monocyte histiocyte ratio During and after treatment a distinct drop in the number of histiocytes is noticeable and this is followed by a gradual restoration of the monocyte-histiocyte ratio to normal Whenever antimony failed to bring about these cellular changes *the patient* showed no clinical improvement

Various compounds of arsenic are used in the treatment of trypanosomiasis and spirochaetal *infections* The mode of action of these preparations seems to be an ind rect one like that of antimony compounds The presence of arsenic within the reticulo endothelial cells has actually been demonstrated by the silver impregnation method Splenectomy experiments in spirochaetal infect ons have demonstrated that infections held

in check in animals break out into acute manifestations in splenectomised animals and that treatment of these with specific drugs is not as effective as in non splenectomised animals There is evidence to show that the mortality rate is increased and the cure rate greatly decreased after splenectomy
necessary for the full therapeutic activi
observations it may be suggested that
serving as a depot for concentrating
of more efficient parasiticidal substances and (c) by increasing the amount of antibody produced and by bringing about destruction of parasites

In Bacterial and virus infections

As regards bacterial infections in acute forms the role of the reticulo endothelial system in the action of potent chemotherapeutic substances discovered during recent years is not clearly understood Possibly they act in the same way as they do in protozoal diseases For virus diseases no drugs have so far been discovered that have any marked specific action on the causative organism Our knowledge of chemotherapeutic drugs used in these diseases is very unsatisfactory The beneficial results that are obtained in virus diseases are chiefly dependent upon the natural resources of the body to combat disease The best we can do in these infections is to help the natural process at work in one way or another This has been attempted with a certain degree of success

In the case of chronic infections a large number of protein substances such as peptone milk, muscle extract vaccines and sera, and certain colloidal metals have been used to stimulate the natural responses of the body Although our knowledge as to how these substances act is still very vague, yet there are reasons to believe that the therapeutic results obtained are probably attributable to a non specific stimulation of the reticulo endothelial system by these substances It has been shown that serological alterations such as increase in titre of antibodies and cellular changes such as leucocytosis and increased phagocytic activity of mononuclear cells, are noticeable after injections of these non specific protein substances There is evidence that these substances are concentrated in organs such as the liver spleen and bone marrow it is likely that through these organs an increase in the efficiency of the natural immune processes occurs

The action of specific anti sera used in the treatment of acute infections is chiefly a direct one upon the causative agent of disease They either destroy the agents themselves or prepare them in such a way that other mechanisms of protection may destroy them subsequently Specific vaccines when injected into the body are probably picked up by the reticulo-endothelial cells and result in the formation of specific antibodies which act as described above

(4) Conclusion

Conclusion

In conclusion we may state that evidence obtained from studies on the mode of action of drugs in infectious diseases taken as a whole strongly suggests that in the overcoming of infections the reticulo endothelial system plays a part of no mean importance The exact manner in which the system responds to the stimulus of treatment appears to depend upon the nature of the infective agent concerned While certain parasites are readily destroyed by phagocytes others require to be disposed of by the destructive action of lytic anti bodies The ideal response in the first case is a mobilisation and functional activation
second
When
o utilise
other methods at its command such as elaboration of powerful parasiticidal
every reason to believe that
factor but rather to a com
plays the predominant part
which is capable of stimulating the natural processes concerned in the cure of disease and in addition bringing about such changes by direct and indirect action on the parasite or its environment as would be conducive to the success of the natural processes at work If this is so then it is easy to understand that a knowledge of the reticulo-endothelial system which is the chief protective mechanism of the body, is essential not only for the proper understanding of infectious diseases but also for the carrying out of successful treatment

CHAPTER V

STIMULANTS AND TONICS

GENERAL STIMULANTS—CARDIAC AND VAS MOTOR STIMULANTS—RESPIRATORY STIMULANTS

Stimulant and Tonic Drugs

The word tonic is commonly used by physicians and by *the laity at large* to denote remedies which stimulate the protoplasmic activity of the tissues thereby increasing the genenal metabolic processes of the body Tonics are generally employed in conditions of asthenia neurasthenia and general depression of the body activities after illness strain and effects of climatic conditions In tropical climates one frequently meets with cases who are victims of chronic maladies *or have become debilitated by living in* a hot and damp atmosphere Good nutritious food and rest combined with tonic drugs go a long way towards curing this condition Tonics produce a sense of wellbeing increased strength and vitality by stimulating the functional activity of the digestive organs as well as by improving the general condition of the hœmopoietic system They contribute towards the improvement of the general tone of the rundown body or some of its component parts Tonics are therefore classed as general tonics *digestive tonics* cardiac tonics hæmatinics nervine or nerve tonics and so on It should be realised however that the convalescent from disease improve more *by adequate rest proper selection of nutritious and easily digestible diet and* good hygienic surroundings than by tonic drugs alone which only aid and *speed up the process*

1 General Stimulants

The drugs classed as stimulants or tonics are very large in number but here it will suffice to discuss only a few of the important ones

Bitters are always prescribed to patients convalescing after long protracted illness where *there is a definite derangement of the digestive functions* and an upset of the general metabolic processes of the body They are used to *improve the appetite of such patients and are generally given before* a meal They produce a reflex flow of the gastric juice which is beneficial to the impoverished *digestive process* The effect of these drugs is never due to direct contact of the drug with the oxyntic cells of the glands in the gastric mucosa but is entirely reflex through the gustatory nerves The common bitter substances in use are gentian quassia and calumba while many of the bitter alkaloids such as the cinchona alkaloids and strychnine are commonly employed for their bitter action in small doses

The preparations of cinchona and quinine are employed in very small doses to stimulate the gastric mucosa they thereby increase secretion improve appetite and aid digestive processes The infusion of cinchona is an excellent stomachic in cases of mild gastric catarrh and atonic dyspepsia The compound tincture in combination with nux vomica is often used as a general tonic and appetiser In all post febrile states in convalescence from prolonged illness in general debility and cachexias from various chronic maladies quinine is often prescribed as a tonic in conjunction with nux vomica iron and arsenic Though *quinine* is believed to be a cardiac depressant the drug in small doses acts as a sedative and by slowing down the pulse improves *the irregularity in rhythm and is* thus beneficial to the heart

Preparations of nux vomica are often prescribed for their simple bitter action They invoke a reflex flow of the gastric juice and tone up the muscular

wall of the viscus thereby improving the appetite and aiding the digestive functions of the patient generally Strychnine is used in atonic dyspepsia and during convalescence from acute illness Besides its bitter properties strychnine is often used as a tonic to the muscular system It diminishes the synaptic resistance in the nervous system whereby a smaller stimulus can pass a greater number of synapses than before and bring into action more nerve fibres It has therefore been used in post-diphtheritic paralysis of muscles and post operative paralysis of the stomach and gut It is a good tonic for sexual debility impotence and spermatorrhœa Strychnine is often reputed as a cardiac tonic but views are very conflicting regarding its direct effect on the heart Experiments show that the drug has no direct effect on an isolated perfused heart in fact it depresses it It is however held that the drug does indirectly improve the heart beat through its stimulating effect on the medullary centres The drug is undoubtedly an emergent cardiac tonic as when injected with atropine in threatening cardiac failure it will almost immediately raise the tone of the organ and strengthen the pulse Injections of strychnine are useful in weakness of the heart in acute fevers such as penumonia influenza and diphtheria It is held that the drug increases the blood pressure by its effect on the medullary centres and in this way improves the nutrition of the myocardium by improving the coronary circulation Strychnine is also a useful respiratory stimulant in chronic bronchitis pneumonia and emphysema Strychnine is a tonic in the real sense of the word in that it increases the tone of all striped and unstriped muscle tissue in the body which is lowered after disease and other debilitating conditions

Alcohol

Alcohol has long enjoyed the reputation of being a good stimulant It is often used in cases of chronic debility and various wasting diseases It has been shown that regular use of moderate doses of alcohol with meals promotes digestion increases appetite checks waste favours deposition of fat and so alcohol practically possesses all the properties of a true food It is a food in the sense that it is readily oxidised yielding considerable energy which is only available for immediate emergency use and cannot be stored as a reserve for future use

Alcohol excites secretion of gastric juice and it can also produce a direct stimulant action on the fundus of the stomach causing an abundant secretion of dilute gastric juice Apart from being a digestive stimulant it is also used as a restorative in urgent cases of fainting or threatening cardiac failure due to shock hæmorrhage etc. Here it acts as a diffusible stimulant reflexly and thereby increases the pulse rate blood pressure and respiration

Alcohol is contained in various tonic wines sold in the market and is often prescribed for convalescing patients It should always be given in small and frequently repeated doses as given in this way it is completely metabolised If larger quantities of alcohol are taken its toxic effect over balance any of the beneficial effects produced

Thyroid

The use of endocrines as tonics is of recent origin They appear to form a system which regulates the rate of metabolism and tha growth and development of the body Thyroid is reputed to be a stimulant of the endocrine glands It has been considered as the trigger gland of the body which sets other endocrines to action Besides its use in thyroid deficiency diseases it is

It is useful to convalescing patients

ied strain and over work In tropics

imate such cases are frequently met

with and the drug in small doses has given encouraging results It acts by increasing the rate at which energy is produced by the body Administration of thyroid adds more fuel to the fire of metabolism in the body and the oxygen intake rises The body machine is geared at a higher level and food normally used to supply the current demand for energy and stored as fat is now used to yield more energy and only a small proportion is reserved for future use Appetite is thus increased patients feel more energetic and the gland now serves the purpose of a tonic in the right sense of the word Thyroid B P known as thyroid siccum should be prescribed in doses of ½ to 1 grain twice daily for this purpose for a period not exceeding a fortnight at a time

Arsenic is believed to be a digestive stimulant when given in small doses (1/50 gr) It has been shown by experiment that arsenic accelerates formation of red blood cells but the effect is slight and unimportant Inorganic compounds have probably no marked therapeutic effects and should not be prescribed

Calcium compounds have a reputation as a stimulant Calcium is a normal constituent of the body tissues and is indispensable to the life of all organisms The calcium content of the body is about 2 per cent of its entire weight In pulmonary tuberculosis calcium injections are said to be useful but there is no rational foundation for that belief Even in urticaria serum sickness and chilblains its efficacy is doubtful though it is largely prescribed Calcium lactophosphate and glycerophosphate with cod liver oil and ultra violet therapy are useful in rickets and malnutrition

Iron is a haematinic It is a natural constituent of the body The adult human body contains 3 to 5 grains of iron in the form of haemoglobin the liver contains 0 15 to 0 25 gm There is no large store house of iron in the body which can be called upon to supply a deficiency though it is believed that the liver and spleen can store considerable amounts From 0 5 to 1 mgm of iron is lost daily in the urine and 5 to 20 mgm in the fæces The amount of iron in an average mixed diet is 5 to 20 mgm a day it is therefore very little more than is necessary to make good the normal daily loss Iron is only prescribed when there is deficiency as in anæmias The tone of the nervous system is improved with iron therapy in cases of mental overwork neurasthenia and neuralgia because it stimulates the body metabolism In combination with arsenic strychnine and quinine it is prescribed with benefit in all forms of debility with or without anæmia and where there is a general lack of tone in the tissues In all conditions where there is loss of appetite and sluggishness of body functions iron therapy is beneficial

us

Phosphorus is the normal constituent of most tissues Its popularity is a relic of the notion that it was a brain food as it occurs in a high proportion in the brain tissues The lactophosphates glycerophosphates and hypophosphites often prescribed as tonics are inactive

2 Cardiac and Vasomotor Stimulants

ical
tions

The circulatory system with the lungs may be regarded as a single functional system which supplies oxygen to the tissues and removes carbon dioxide from them They are efficiently controlled according to the needs of the body from time to time by a central ... The heart forms the central and the most important organ ... without ever ... contractions ... seases The ... he patient in capac y o ... by its unique disease all depend on the condition of the heart ... properties—namely automaticity or stimulus production rhythmicity excitability contractility tonicity and conductivity

The heart has the first call of blood leaving it by the aorta and as much as 20 per cent of the total output may enter the coronary circulation Unlike voluntary muscles, [illegible] ...ncy in oxygen supply to its need [illegible] ...pressing and injuring the efficacy [illegible] impoverish heart from lack of [illegible]

The heart has great reserve power to meet the demands of emergencies and [illegible]

[illegible] it to 1 litre.

The [illegible] the vagus [illegible] of contra[illegible] auricle t[illegible] depresses the force of beat of the auricles and also the rate of conduction from the auricle to the ventricle. The vagus has a constant control over the activity of the heart the control is slight at two extremes of life and maximum in early adult life The vagus also constricts the coronary arteries and the sympathetic dilates them In spite of the regular and constant nervous control over the heart's activities, the pace maker of heart has a natural rhythm, irrespective of any nervous control

The demand of the tissues for oxygen varies from minute to minute and this is regulated by the blood flowing through the small arteries and the arterioles The distribution of the blood is so efficiently made that the organs, whose continuous activity is most essential to the maintenance of life, receive the major share most promptly and regularly Arrest of circulation in the brain only for a few seconds will result in unconsciousness The brain regulates the general supply of the blood to other organs after ensuring a rich supply for itself The body mechanism is so adjusted that the demand for blood supply is met in emergent cases for some particular functioning organ at the expense of the other This is met with by a proper regulation of the arterioles mostly by a central and a peripheral mechanism. The arterioles are very richly supplied with vasoconstrictor nerves and by their action as well as by the vagal and vasomotor centres in the medulla, the general blood pressure and the supply of blood to different organs of the body are determined. The arterioles supplying the most vital organs of the body the constant activity of which is most essential to life, are not supplied by the vasoconstrictor nerves The arterioles terminate in thin walled capillaries which perform rhythmic contractions At rest only a small number of them dilate to carry on the circulation to distant parts while when an organ functionates, the arterioles supplying it dilate and a greater number of capillaries open, and the blood flow to the organ increases manifold The normal circulation of the blood depends on the maintenance of a certain amount of tone in the capillaries and the veins, failing which the blood stagnates and the heart does not receive adequate quantity of blood to contract upon and to carry on its proper function

The splanchnic vessels are richly furnished with vasoconstrictor nerves, and next come those supplying the skin and the muscles. It is stated that the blood flow through the skin and muscles at rest is 12 10 ccm, per 100 gm, per minute liver and kidney 70 ccm, brain 150 ccm and the endocrines 600 ccm

The failure of the heart to maintain an efficient circulation in the body is not an uncommon complication in diseases From the clinical point of view the following types of cardiac failures are met with

(1) Acute cardiac failure causing sudden death, it occurs in angina pectoris ventricular fibrillation and coronary disease Acute failure is also produced by chloroform, lightning or electrical shock.

(2) Sub-acute cardiac failure occurs in acute infectious diseases e.g., pneumonia, typhoid, diphtheria, influenza, etc.

(3) Chronic cardiac failure usually occurs in chronic valvular disease and myocardial lesions

In considering the treatment of heart failure it should be remembered that the [illegible] cause of heart failure lies in the heart muscle

The treatment of heart failure may be conveniently described [illegible] following heads

When the heart is compensated careful instructions should be given to the patient regarding his mode of life It is of vital importance that he should have abundance of physical and mental *rest in his daily life* Excitement anxiety worry and emotional strain should as far as possible be avoided He *should not have any physical exertion* that would give rise to breathlessness palpitation fatigue a sense of tightness across the chest or precordial pa n At the same time a certain amount of graduated exercise is desirable Walking on the plains is preferable to hill climbing *When the cardiac affection is progressive* the amount of exertion must be correspondingly reduced With regard *to diet the food should be nutritious easily* assimilable and not likely to cause indigestion A carbohydrate diet is bulky and apt to ca diet increases the resistance in the periphera refore be a mixed one with predominance of the albuminous element A careful search should be made *for a septic focus which should if possible be eradicated* The bowels should be kept open and regular

The underlying idea of treatment with drugs should be (*a*) to give rest to the heart as much as possible (*b*) to improve the nutrition of the heart (*c*) to increase the force of systole and prolong diastole thus improving the efficiency of the contractions and lengthening the period of rest There is a great deal *of confusion as to what* *to the heart* The word cardiac tonic eased activity or tone is being brought while cardiac stimulant means a prompt but transient increase in the activity of the heart which is not enduring The idea of treatment of heart d sease is not to increase *the frequency* of a failing heart because thereby the process of exhaustion is hastened During the compensated stage no cardiac tonics are required

Digitalis is the most useful drug for failing compensation In the words of Mackenzie *Digitalis acting on the vagus pulls the reins of the* heart acting on the heart muscle it is a most useful whip at the same time provid ing it with food by improving the circulation By slowing the heart it makes it regular and also this gives the heart an opportunity of resting so secondarily improving the contractility conductivity and excitability of the organ

Lewis writes The giving of digitalis to unselected heart cases is much to be deplored Those who regard digitalis as a *cardiac stimulant mistake its* character its chief action is to rest the heart To the heart foxglove is not tonic but powerfully hypnotic It controls the diastole of the heart it extends the period of ventricular sleep

There are two conditions in which digitalis is indicated (1) Heart failure specially of the congestive type with cardiac dilatation diminished contractility and tor Mitral cases with water logging ventricular rate exceeding 80 per sence of a chron c auric lar fil rillat ot supervened Such cases may be kept going and heart failure postpo ... initely by adequate d gitalis *medication* directed to maintain the ventricular rate below 80 per minute at rest Provided congestive heart failure is present hypertension and aortic regurgitation are *not contraindications* as was *formerly* taught The results however in the above two conditions as well as in agina pectoris are not always as favourable as in the mitral group

Patients put on digitalis for the first time, should go to bed and remain there until the reaction to the drug has been investigated fully As a routine the tincture of digitalis biologically standardized is used A usual and safe dosage for an adult is 60 to 75 minims of the tincture daily, by mouth But in India and warm climate leaf powder should be preferred The tincture may be given divided into two or three doses diluted with water, and not mixed with other medicines

Digitalization

According to Eggleston the average amount of the drug required to digitalise the human heart is 9/40 grain of the powdered digitalis or 2¼ minims of the tincture p r pound body weight In estimating the weight, the amount of fat and œdema must not be taken into account In non urgent cases, one-fourth of the calculated dose is given at once, one fourth after six hours and thereafter one-tenth to one eighth of the total every six hours But in urgent cases, one third to one half is given at once, six hours later one fifth to one fourth and after another six hours one-eighth to one-sixth

Th e ma n that th ...

of the tincture One half or one third of the total dose is given at once and the remainder two portions after an interval of four to six hours in urgent cases If digitalis has been taken within the previous fortnight it is best to give 0 2 gm (0 16 USP XI) of powdered leaf three or four times a day, the patient being carefully observed for toxic effects before a subsequent dose is given It usually takes 6 to 8 hours for a single dose to take effect

The Eggleston method of heavy dosage and rapid digitalization is reserved for the cases in ext[illegible] patient can be examined at least t[illegible] 60 minims of the standardized tir[illegible] esired slowing of the heart rate is [illegible]

Digitalis lanata

In recent years *Digitalis lanata* has come into use It is a potent source of glucosides stated to be nearly 4 times as potent as *D purpurea* *D lanata* contains four glucosides, of which the chief is lanadigin It is only one third as toxic as strophanthin it accumulates in the body more than strophanthin but much less than the purpurea glucosides Clinically, it is said to act more rapidly than any of the purpurea preparations and the nature of action is similar

For interavenous medication digoxin BP is best Digoxin is pure glucoside isolated from the leaves of *digitalis lanata.* It is a pure glucoside of constant composition and is slightly soluble in water The drug is marketed in ampoules each containing 0 5 mgm in 1 ccm of 70 per cent alcohol This is mixed with 10 ccm of normal saline and given intravenously slowly at least 2 minutes being taken Full effect occurs in 2 hours after which the dose may be safely repeated if the ventricular rate has not been slowed enough The initial dose should be 0 5 or 1 mgm The maintamance dose is 0 5 mgm a day orally

Strophanthin

Strophanthin has the same action as digitalis, the standard tincture of [illegible] urs but the effects are unreli[illegible] P is given in doses of 0.25 [illegible] The initial dose of 1 mgm is roughly equivalent to about 6 ccm of the B P tincture of digitalis When the urgency has passed off, digitalis can be given by the mouth. Caution has, how

ever, to be exercised, as the drug sometimes behaves in an unaccountable manner, loss of consciousness has followed an ordinary dose in a weakened patient It should always be well diluted with 10 ccm of normal saline, and injected, very slowly, *into the vein* In acute febrile heart failure, sudden death has rarely occurred with intravenous strophanthin

Camphor is now a days largely used in the treatment of heart failure especially in chronic myocarditis with simple cardiac insufficiency In typhoid and pneumonia it is considered as a valuable stimulant to the heart With regard to its effect on the heart, no decisive and accepted proof has been obtained of any direct action on the organ *Given subcutaneously, camphor acts as a local* irritant and reflexly stimulates the medullary centres The evidence available suggests that it does not directly stimulate the heart, but like alcohol causes redistribution of the blood, which will benefit the patient generally and the heart beat particularly It is now generally employed in doses of one to one and a half grains, dissolved in 1 ccm of ether or olive oil, and injected hypodermically

Nikethamide is popularly known under the proprietary names of coramine nikamide and anacardone, cycliton is an allied drug For injection, niketha mide B P is used as 25 per cent solution in water Nikethamide is absorbed if given orally, but stimulatory effects are best obtained when given intravenously Besides its general stimulating effects on the central nervous system it has a marked stimulating effect on the respiratory centre There seems to be little support for the claim that in repeated doses it is of value in the treatment of myocardial diseases

Proprietary names of leptazol are cardiazol phrenazol, hexazol triazol azoman *Metrazol is the official name in the U S P Injections of leptazol* B P is a 10 per cent solution in water, dose 5 ccm to 10 ccm Leptazol is absorbed when given by the mouth The effective dose in narcotic poisoning is from 3 to 5 ccm of the injection given initially, the dose is increased until the patient responds or convulsions are produced

Caffeine is a direct cardiac stimulant acting on the excito motor area of the heart It produces an increase of the pulse rate, but from the point of view of rational treatment, stimulation of the heart alone will be of little value unless the circulation is improved as well, its efficacy is therefore doubted Caffeine sodium salicylate or caffeine sodium benzoate in doses of 2 grains may be injected subcutaneously to produce stimulation of the heart But this action is of relatively little value, because in a failing heart, the increase in frequency leads to exhaustion

Adrenalin is a peripheral sympathetic stimulant *It augments and accelerates* the cardiac beats and is one of the most potent therapeutic agents to resuscitate a *failing heart* Adre ... intravenously, especially by the latter r ... pres sure, and consequently ... heavy strain on the heart and ... alin is transient and except in ... feeble heartbeat no permanent ... t has however been used in threatened or complete arrest of the heart, when that is not due to fibrillation Intravenously, adrenalin acts almost immediately The dose should be about one-fiftieth of that of the hypodermic dose, and there is no remedy available that bears comparison with it in such cases Intracardiac adrenalin to resuscitate the patient in cases of arrested heart beat or in anæsthetic

syncopy, has been tried The dose of adrenaline by the subcutaneous route is ½ ccm or less It is stated that 3 to 5 minims is the optimum and effective dose even in severe spasms of asthma, higher doses than ½ ccm cause shock, rigor, and profound bodily tremors and depression for many hours after For intravenous purposes, a dose of 2 minims diluted with 2 ccm of distilled water is given very slowly Under no circumstances should adrenaline be used in ordinary cardiac failure, as it puts extra strain on the heart by increasing peripheral resistance by vaso-constriction

Adrenalin is very unstable in neutral or alkaline solutions and in such solutions it is very readily oxidised to form inert substances The solution turns brownish with age and the deterioration in potency is proportional to the discoloration and any solution thus discoloured is unsuitable for use.

Ephedrine The vaso-pressor effect of Ephedrine is now well recognised It is used by some clinicians to guard against heart failure in pneumonia and influenza, ¼ to ½ grain three times daily is given in cases of low blood pressure The advantages of ephedrine over adrenalin are that it can be given by the mouth and produces an action of much longer duration The toxic effects of the drug should, however, be borne in mind

Chopra and co-workers had shown that pseudo ephedrine has a direct stimulant action on the myocardium A tincture made from ephedra, which contains both ephedrine and pseudo ephedrine, has been used with success in epidemic dropsy, *pneumonia, diphtheria, etc , the usual dose is 15 to 20 mins thrice daily*

Glucose It is a valuable agent in heart failure When given intravenously after leeching or venesection, it acts as a food to the heart and stimulates the function of the kidneys The details of therapy are given elsewhere

Cane-sugar is considered to be a valuable cardiac nutrient In the body, it is first converted into glycogen and thence to glucose, and as such serves as a source of food for the heart muscle in conditions of prolonged strain in some acute fevers, as pneumonia, influenza, typhoid as well as in cases of chronic cardiac failure The average adult dose for the sugar is 4-8 ounces a day

Oxygen It has been found very useful in cardiac disorders with hypertension arteriosclerosis, aortic insufficiency, etc It is administered in form of oxygen bath 90° to 95°F (32°—35°C) It lowers the blood pressure, and there is a coincident diminution in the size of the heart These effects persist only a few hours after the first bath, but after 15 to 20 baths, very prolonged and even permanent physiological and therapeutic effects are obtained They are contra indicated where the blood pressure is much below normal, especially if associated with mitral defect and profound anæmia

3. Respiratory Stimulants

Carbon dioxide is a respiratory stimulant *par excellence* Addition of 1 per cent of CO_2 to the inspired air increases the volume of air breathed per minute by 25 per cent 3 per cent CO_2 increases it 100 per cent, and 6 per cent increases it from 500 to 600 per cent *Carbon dioxide* Carbon dioxide, however, should not be used indiscriminately and like other potent remedies may prove a dangerous weapon if used without reasonable care Lower respiratory centres are not stimulated by CO_2 and therefore under certain conditions harmful effects rather than beneficial may result by increasing the concentration of CO_2 in the inspired air

Inhalation of oxygen containing 7 per cent CO_2 acts as the most powerful respiratory stimulant and is the method of choice in a variety of conditions—such as drowning CO poisoning in apnoeic new born infants and in morphine poisoning *If the respiration has been totally arrested inhalation of this mixture should be forced* by artificial respiration Prolonged periods of unconciousness following anaesthesia injury or poisoning with narcotics and abdominal injuries which inhibit the cough reflex lead to blocking of bronchi with mucous plugs This may be followed by atelectasis or massive collapse and then pneumonia For the prevention of such conditions inhalation of a mixture of above proportions is most valuable and is recommended to be used as a routine measure after prolonged operations

All general nervous stimulants such as caffeine strychnine coramine and cardiazol stimulate the respiratory centre and are particularly indicated when the respiratory centre becomes insensitive to rise of CO_2 tension in the blood Coramine and cardiazol are very popular in treatment of patients in extremis Caffeine is a very strong respiratory stimulant distinct increase in the rate of respiration and volume of air breathed and a clear diminution in the pressure of CO_2 in the alveolar air following its injection

Peripheral stimulation by several means such as flicking with a wet towel (especially used for apnoeic new born or morphine poisoning) chloroform inhalation injection of camphor etc also excite the respiratory centre

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CHAPTER VI

PAIN AND INSOMNIA

INSOMNIA AND THE USE OF HYPNOTICS—HYPNOTIC AND ANALGESIC DRUGS—PAIN AND ITS CAUSATION—OPIUM DERIVATIVES AND OTHER ANALGESICS

1. Insomnia and the Use of Hypnotics

Aetiology of sleep

Sleep is one of the primary necessities of human life It is a natural state which normally comes on when an animal ceases to attend to external or internal stimuli the reflex activity of the central nervous system is inhibited to a degree which is normally accompanied by unconciousness Falling asleep is the natural consequence of keeping awake

Loss of sleep or prolonged deprivation leads to many pathological changes in the body Normal sleep is a protective mechanism by which the physiological wear and tear of the body are made good It appears at definite times and if unsatisfied will pass off, but frequent abstinence leads to permanent derangement of body function Prolonged sleep lessness causes various pathological changes such as histological changes in the cerebral cortex and probably the appearance of a toxin in the blood

Sleep is a condition of unconsciousness to surroundings There are many theories as to the etiology of sleep Muscular relaxations rise in the intra cranial pressure cerebral anæmia and similar other theories have been advanced Cerebral anæmia will undoubtedly produce unconsciousness and sleep but the natural sleep is not however attended with any material alteration in the cerebral circulation Knowledge regarding the mechanism of sleep is still very scanty The nervous system acts as a whole Pathological and experi mental lesions in the infundibular region produce pathological sleep A diencephalic sleep centre has been described but the term waking centre would be more appropriate Presence of sleep suggests an abeyance of the katabolic activity associated with the sympathetic system and an excess of the anabolic activity associated with the parasympathetic system The diencephalic centre is stimulated by sensory impulses from many directions Insomnia might be due to excessive cortical activity and for this there is no need to use drugs strong enough to depress the diencephalon.

Others regard sleep as a rhythmic depression of the activity of the brain and insomnia as due to one or a combination of two causes abnormal afferent stimuli affecting the [illegible]

stimuli as worry

Common causes

The common causes of not sleeping are —(1) Pain which can be relieved by 1/4 gr of morphine (2) Mental and emotional excitement or excitement caused by moderate doses of narcotic drugs (3) Dread of non sleeping which is cured by restoring the confidence of the patient (4) The no sleep habit which should be corrected.

There are different types of insomnia with different causes and treatment for one type may not be suitable for another Some persons are light sleepers from their infancy in others the ability to sleep has been lost from overwork, sorrow or worry or after a severe illness or nervous breakdown Women may get insomnia when they get sleep less nights in bringing up children from nightly waking Some individuals do not sleep when they go to bed while others fall asleep and wake up with a start and gradually lose the desire to sleep Others awake between 2 and 5 in the morning or awake and drowse throughout the night Still others are more or less asleep all night but are not sufficiently rested because they are tossing about or have bad dreams

The commonest cause of sleeplessness is mental fatigue and muscular or nervous tension the brain remaining active This is particularly the case when intense mental work is being done in the course of the evening Many people start worrying about not getting sleep when they go to bed. They are so much afraid of insomnia that they keep themselves awake Some live in noisy streets and cannot sleep on that account.

Inhalation of oxygen containing 7 per cent CO_2 acts as the most powerful respiratory stimulant and is the method of choice in a variety of conditions—such as drowning CO poisoning in apnoeic new born infants and in morphine poisoning If the respiration has been totally arrested inhalation of this mixture should be forced by artificial respiration Prolonged periods of unconciousness following anaesthesia injury or poisoning with narcotics and abdominal injuries which inhibit the cough reflex lead to blocking of bronchi with mucous plugs This may be followed by atelectasis or massive collapse and then pneumonia For the prevention of such conditions inhalation of a mixture of above proportions is most valuable and is recommended to be used as a routine measure after prolonged operations

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Others regard sleep as a rhythmic depression of the activity of the brain and insomnia as due to one or a combination of two causes abnormal afferent stimuli affecting the brain at a time when its depression is due or increased excitability of the brain cells The rational treatment of the first type is to remove the stimuli if possible Increased excitability may be congenital or acquired there are brains which are easily kept awake from childhood Excitability can be increased artificially as by caffeine ephedrine and high blood pressure Bromides are especially valuable for normal brains kept awake by such stimuli as worry

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If a person suddenly develops insomnia without any apparent cause think of hyperthyroidism or encephalitis In other persons it may be due to arteriosclerotic injury to the brain Psychopathic individuals heading for a nervous breakdown do not sleep for fear of night mares

The treatment of insomnia is of importance Many of the chronic invalidating diseases, such as chronic malaria, kala azar, ankylostomiasis are accompanied by loss of sleep and the practitioners are confronted with the problem of procuring rest for the body, in addition to finding some specific remedy for the malady The use of hypnotics is not, however, always indicated and treatment may be described under two heads

For minor ailments, such as flatulence and distension of the stomach no hypnotic drugs are called for, careful regulation of the dietary together with some gastric sedative will relieve the condition and help to produce sleep In cases where the specific cause of sleeplessness is untraceable, a careful survey has to be made as regards any unusual mental stress or strain which may be responsible for the loss of sleep

General hygienic measures, regular and careful dieting exercise in the open air without involving any physical fatigue, will be effective in those cases where insomnia is due to overwork and prolonged mental exertion A holiday in the country, in the hills, or at the seaside are often the most successful remedy, although some hypnotic may be necessary some time or other to supplement the effect Besides conditions that favour relaxation, *viz*, a quiet room, and a suitable bed will be of great help

There can be no real cure for insomnia unless the patient can reduce the hours of mental work especially night work When insomnia is bad it may be wise to go to bed an hour earlier than it is intended to sleep During the first few minutes after the light is turned out, all thinking about problems, worries and activities should be stopped and mind concentrated on going to sleep Every bit of will power will be needed to keep out of mind all disturbing thoughts which produce tension The mind should be filled with thought which relieve tension Listening to or reading an unexciting book may be helpful The physician should impress on the patient that insomnia is nothing terrible, there are thousands of people who enjoy good health and work hard who have not slept for years The patients may possibly be sleeping on a chair for hours and imagine they have slept only for a very short time

Patients with indigestion sleep better if they take a very light meal at night Some people sleep if they take a warm drink before retiring Alcohol is often an excellent sedative and induces sleep, especially in older persons Older people who have to get up at night to urinate should cut down the amount of liquid in the afternoon and evening

Drugs should be used when necessary without hesitation if person is likely to suffer from the effects of insomnia next day Habituation though it occurs is met with in a class of indisciplined people If after a few minutes the person feels that his brain is very active and that sleep will not come, and if stress of next days work make it essential a rapidly acting barbiturate (*sodium luminal* ½ to 2 gr) may be taken These drugs do not produce euphoria like opium derivatives and a habit is less likely to be formed The physician should have a thorough knowledge of action of sedative drugs and should prescribe the drug best suited for a particular case when it is essential In psychopathic persons, barbiturates are ineffective and produce terrifying night mares

2. Hypnotic and Analgesic Drugs

A hypnotic is a narcotic drug which is used to enable the patient to get the sleep which is due to him or desired by him

Ideal hypnotic

According to Clark the properties of an ideal hypnotic are —(1) The drug must produce a reliable hypnotic effect (2) The hypnotic action must be produced without a preliminary stage of excitement (3) The drug must not irritate the stomach (4) The
ar interval
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, and does
ot produce
dangerous side actions, such as cardiac depression. (7) There must be a sufficient margin of safety between the dose required to produce hypnosis and that which produces medullary depression. (8) The drug must not produce tolerance, nor a drug habit, when given regularly over long periods

There is no drug which possesses all these qualities together and it is only after prolonged use that some of the disadvantages are found out. Drugs of low toxicity include the inorganic bromides (*e g* sodium, potassium ammonium, strontium and calcium bromides), alcohol, phenazone and its derivatives aspirin and salicylic acid derivatives, barbituric acid derivatives, etc

Analgesics might produce sleep by reducing afferent stimuli and can be usefully combined with hypnotics but a fixed inflexible combination is dangerous A small analgesic dose of morphine combined with chloral might be more effective than a large dose of the either drug alone Combinations of hypnotics acting at different points are also useful Salicylates have a special property of diminishing painful stimuli and thus act secondarily as hypnotics

The abuse of hypnotics Serious dangers in connection with the use of hypnotic drugs are well known They are liable to produce habit formation and the patient may be unable to sleep without his customary dose Addiction to the drug may result and this is more serious as increasing doses are necessary to produce the desired effect

Automatism

Automatism may result from a small dose dulling the patients intelligence and he may forget that he has already taken a dose and may only remember his intention to do so In this way patients have been known to empty a whole tube of tablets left by their bed side, with consequent disasterous results If such a person awakes at all he may have no memory of his performance.

The following are some of the hypnotic drugs which are commonly used —

1 *Alcohol* The effect obtained is proportional to the patients previous abstinence a strict tee totaller falling to sleep with a small dose whereas a habituee requires much larger doses For a patient unaccustomed to alcohol a mild hypnotic dose is about 20 to 30 ccm equivalant to about 1 to 2 ounces of whisky or brandy

rectum The dangers of depression of the heart and respiration with chloral are over rated and it can be considered a safe hypnotic if it does not overstep the therapeutic limit

The average poisonous dose of chloral is about 90 grains, but death has been recorded after 30 grains. The safety margin of chloral is therefore, variable The drug should not be used for control of convulsions or for any condition requiring the full narcotic dose of about 75 grains,

Action of chloral hydrate

The action of chloral resembles barbitone and the sleep usually comes on peacefully and without any unpleasant side effects. The effect of a big dose of chloral, however, does not persist so long as a big dose of a stable barbiturate, chloral being more rapidly destroyed in the tissues The effect of barbitone and phenobarbitone may last for more than 24 hours but that of chloral for 12 to 18 hours Chloral cannot be kept in form of compressed tablets which is a disadvantage, but it is a mild rapidly acting hypnotic. It is often given in combination with opium and bromides for restlessness in early stages of acute fevers, such as, pneumonia. The *three fifteens* is a popular draught containing 15 minims of tincture of opium, 15 grains of chloral hydrate and 15 grains of potassium

bromide In painful illnesses where the brain is excited by worry or toxins of fever it prevents sleeplessness

[illegible] (during teething) and small chil [illegible] Chloral addiction is rare Dri [illegible] (or formamide) which are not [illegible] ocal and anaesthetic action on [illegible] is 15 to 20 grains

Combination of chloral and camphor forms a liquid paste which evaporates when applied to the skin and has a pain relieving effect

3 *Paraldehyde* It produces natural sleep in 15 to 20 minutes lasting for several hours *but the effect of the drug is less certain than chloral hydrate and it has no analgesic* action It is said to produce no depressing effects on the heart and respiration in therapeutic doses and can therefore be safely administered in cases complicated with heart disease The disadvantages of the drug is that it has got a very unpleasant taste which however, can be rectified by giving it in some flavouring agent Prolonged use of paraldehyde leads to irritation of the throat and stomach an unpleasant odour in the breath, dizziness and faintness, and a habit not unfrequently develops

The dose of paraldehyde for single administration is one drachm (4 ccm) and in some cases two drachms may be given In cases where the drug has to be given repeatedly one teaspoonful every hour should be given till sleep is produced

Paraldehyde dissolves in 9 parts of water *It is given floated on top of some water* or some strong tasting substance such as liquorice extract to disguise its nasty burning taste It freezes at about 52°F and forms crystals

Paraldehyde when taken by the mouth is rapidly absorbed and rapidly excreted mainly by the urine but partly by the lungs Death has occured with two ounces but such doses *are not always fatal With 60 to 1* [illegible] produced in an adult in 5 to 15 mi [illegible] arouse and he may go on sleeping f [illegible] in pain he may remain half asleep a [illegible] toxaemias such as that of pneumonia

Paraldehyde is prescribed in delerium tremens as it may send the patient to sleep and because of its nasty taste it is not likely to form a habit It is used as a basal narcotic in doses of one drachm (4 ccm) per stone of body weight.

4 *Tribromoethyl alcohol* This is a white crystalline powder unstable in air Bromethol B P goes under the proprietary name of *Avertin*. It is a solution of 1 0 gm of tribromoethyl alcohol in 1 ccm of amylene hydrate It decomposes in presence of light giving off hydrobromic acid which is an intense irritant Acidity of solution should be tested before use and if the pH is higher than 3.0 the solution should not be used

The drug is moderately rapidly broken down in the liver When given per rectum maximum effect is attained in about 30 minutes The dose should be proportionate to the body weight varying from 0 06 gm to 0 12 gm per kilo according to the degree of the effect desired *No matter how heavy the patient more than 10 gm should not be* given as a single dose It is not recommended per rectum Intravenous injections produce a profound narcosis In preparing solutions for rectal injection the temperature should not be raised more than 50°C (122°F) as it decomposes and produces severe ulceration

Toxic effects are rare though necrosis of liver has been observed after repeated administration in tetanus As a basal narcotic it is safer than barbiturates but less safe than paraldehyde

5 *Sulphone Group* The drugs belonging to this group sluphonal trional and tetronal are insoluble slowly absorbed and slowly excreted and dangerously cumulative producing hematoporphyrinuria These have been entirely discarded

6 *The Barbiturates* Although urea has no n [illegible] atoms in its molecule produces narcotic properties Barbit [illegible] of urea and malonic acid It is unstable and has [illegible] ious side chains to its molecules, however confers [illegible] its compounds

Mode of action

The mode of action of all barbiturates is the same the difference being only in dosage The persistence of effect depends on the stability of the compound which again depends on the rate at which the side chains undergo oxidation The kidneys excrete the stable barbiturates, in disease of this organ excretion is diminished and narcotic action may be prolonged The oxidation of unstable barbiturates taken place in the liver and in the disease of this organ these compounds are more, dangerous than usually, they may produce prolonged narcosis and death Even stable barbiturates may be decomposed by the liver in small quantities

Tolerance

In case of unstable barbiturates a little tolerance is acquired but in case of stable compounds a fair amount of tolerance is acquired, this power probably depending on the increased power of the liver to oxidize these drugs Tolerance is only slowly acquired and, therefore, moderate repeated doses may produce cumulative results

Barbituric and allied acids are poorly soluble in water but their sodium salts are soluble and are administered by injection Barbiturates have no local irritant effect or remote toxic effects on the viscera Instances of marked idiosyncrasy are not uncommon the effect produced being more profound and prolonged A large dose should not be given without testing for idiosyncrasy Barbiturates are divided into two groups —

(i) *The stable barbiturates* The stable compounds are slowly decomposed in the tissues and exert a prolonged effect Such compounds are —Barbitone B P veronal (diethyl barbituric acid) which is insoluble Dose 5 to 10 grs Its soluble sodium salt—soluble barbitone B P, or medinal—dose 5 to grs

Phenobarbitone B P or luminal or gardenal which is insoluble Dose ½ to 2 grs Its sodium salt which is soluble sodium luminal Dose ½ to 2 grs

Dial or allobarbitone B P C Dose ½ to 3 gr

These compounds are slowly destroyed 90 per cent of barbitone given by the mouth is recovered from the urine The barbiturates of the second group cannot be recovered from the urine The [illegible]
The B P dose should
a quarter of that m
Repeated doses may p
itchy and papular, oe
confusion and even motor paralyses

Luminal is a very useful drug in epilepsy being superior to bromides It produces less mental dullness Dose 1 to 4 gr a day

(ii) *Unstable or short action barbiturates* which are rapidly decomposed in *the fever* and their action lasts from 4 to 6 hours

Butylethyl barbituric acid or butobarbital or soneryl Dose 1½ to 3 gr (0 1 to 0 2 gm)

Pentobarbitone or nembutal Dose 1½ gr or less (0 2 gm) Other compounds with similar action are hebaral pernocton phenodorm seconal, sodium salts are used in the same dosage when soluble salts are required They are prepared in cachets to guard against decomposition

Barbiturates of this class are the best hypnotics for insomnia They are readily absorbed, leave no sleepy feeling next morning and repeated administration is not followed by toxic symptoms and tolerance is not readily established

Barbiturates of this class are used as basal narcotics They are also useful where repeated dosage are required as for convulsive states

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Many proprietary remedies are on the market which contains an analgesic such as amidopyrine and a narcotic, usually a barbiturate.

habit formation and for this reason its sale is prohibited in U S A *It is recognized by the B P as diamorphine hydrochloride*, dose 1/24 to 1/8 gr It is rarely if ever prescribed

Apomorphine is another morphine derivative It has a slight hypnotic action after initial vomiting has passed off *It has a selective action* on the vomiting centre and is used as an emetic.

Morphine in relief of pain Morphine and heroine surpass all other drugs *in relieving pain* Amidopyrine and the salicylates possess a definite selective action on the pain centre but their action is very mild, increase *of dose do not* increase their analgesic effect local applications such as warmth local irritants have also a limited effect It is essential that the *practitioner should distinguish* between the minor pains capable of being relieved by aspirin, phenacetin amidopyrine etc from severe pain *which can only be relieved by* morphine

The acute pain due to the disease of the heart can only be relieved by morphine When the pain is due to coronary *occlusion and the patient has to be kept at rest, morphine should be* given in adequate doses It should also be given in dyspnoea of heart disease *whether accompanied by* pain or not In paroxysmal attacks of dyspnoea due to failing left ventricle morphine gives relief on account of its depressant *action on the respiratory* centre slowing of the rate and depth of the respiration tend *to relieve the added strain* which dyspnoea throws on *the heart The relief afforded* in these cases is dramatic with a dose of 1/4 gr or less In early stages of lobar pneumonia the pain is often severe *due to pleuritis* and morphine is indicated Morphine also relieves irritative cough of tuberculosis of lungs in very small doses 5 minims of 1 per cent solution of morphine hydrochloride (1/22 gr of morphine) keeping the patient quiet for the whole night

Morphine in insomnia 1/4 grain dose may send the patient to sleep but there may be preliminary excitement accompanied *by nausea lasting for* some hours Although morphine will certainly give sleep to most of these who are in pain it is an uncertain hypnotic in painless conditions

[illegible] the kidney, the excre [illegible] dose of 1/4 grain [illegible] ities will remain in [illegible] nausea and vomiting. After a very large dose *e g* one grain the subject [illegible] of coma for about six hours, after that there is no risk of death by failure of respiration though the subject may remain unconscious for another twelve hours and *very sleepy for a day or two longer*

The official B P dose of morphine is 1/8 to 1/3 gr Such doses may be fatal in the very young or very old on the other hand 1/3 grain may not relieve severe pain in heavy patients A safe initial dose should, therefore be given *at first and if necessary* more should be given till desired effect is produced Repeated dosage is often not necessary *In an average* sized adult 1/6 to 1/3 *grain will relieve* severe pain In vigorous adults free from respiratory embarassment over one grain may have to be given In very young and very old it should be given with the greatest of caution

The following table from Clark (1933) gives the expert report of the League of Nations (1931) about certain morphine derivatives

Drug	Mean *therapeutic* dose in grammes	*Relative* toxicity	Relative *power of* producing addiction	Relative *action* as analgesic	Relative depression of respiration and cough	Relative *depression* of gut movement
Morphine	*0 02* gm	*1*	1	1	1	*1*
Codeine	0·04 ,,	[illegible]	very slight	very slight	[illegible] to [illegible]	[illegible]
Heroin	0·005 ,,	5—10	2—4	2	2	very slight
Dicodide	1·005 ,,		[illegible]	?	1	?
Dilaudide	9·003 ,,		[illegible]	1	[illegible]	very slight

Pethidine Pethidine (*1 methyl 4 phenylpiperidine*) also known as *Dolantin* or Demerol is a comparatively newer addition to the list of analgesic drugs Chemically it is related to drugs highly reputed as pain relieving agents like morphine and tropic *acid series of antispasmodics*

Pharmacological investigation ... affect the pupil or the pulse rate Its toxicity is relatively low, it d ... large doses It thus appears tc ... clinical trials are still needed before coming to definite conclusions.

Pethidine has been given some trials in obstetric cases renal and biliary colics in pain due to injury or operation and in neuralgias The results of these trials are very encouraging In obsetetric cases particularly it has proved successful in relieving pain without any adverse effect on the mother or child

An ideal analgesic should be rapid dependable safe having no adverse side effects and without tendency to habit formation Pethidine can be administered by mouth as well as parenterally and within 5 to 15 minutes of intravenous administration analgesic effect lasting for 3 hours ensues Undesirable side effects such as nausea vomiting or vasomotor disturbances may occur but are mild and of short duration There is no cumulative effect However the withdrawal syndrome although mild does follow on stopping pethidine after administration for sometime and the drug carries certain risk of addiction. In Germany indiscriminate use of this group of drugs has already been stopped

Aromatic analgesics

A large number of coal tar derivatives are commonly used to lower temperature and to relieve headache and pain They have analgesic effect against neuralgic and muscular pains headache, migraine cold etc but are often ineffective if the pain is due to some injury

Aspirin

Aspirin (acetyl salicylic acid) is the most popular remedy for headache in doses of 5 to 15 grains Nothing very definite is known as regards the etiology of headache A rise in the pressure of the cerebro spinal fluid is a frequent cause of headache while the spasmodic contraction of the cerebral vessel may probably be responsible for migraine The manner in which these drugs act is uncertain and Barbour believes that acetyl salicylic acid causes a transference of water from tissue into blood and thereby relieves headache The depressant effect of the drug on the heart precludes its continuous use Phenazone or antipyrin and phenacetin were formerly used as analgesic to relieve headache, migraine facial neuralgia, etc but they are now less frequently used Pyramidon or amidopyrin acts similarly to phenazone and is effective in doses of 5 to 8 grains It is an efficient analgesic and its toxicity is very low Veramon is a combination of amidopyrin with diethyl barbiturate and is said in ... a combination of allyl isopropyl ... hypnotic effect Cibalgin a com... 4 to 16 grains Compral a new a... urethane for use in pain generall...

Veramon

CHAPTER VII

PYREXIA

REGULATION OF BODY TEMPERATURE—PYREXIA AND ITS TREATMENT—ANTIPYRETIC AND ANALGESIC DRUGS—TREATMENT OF FEVER—EFFECTS OF HEAT (HEAT STROKE)· HYPERPYREXIA HEAT EXHAUSTION, HEAT CRAMPS, PRICKLY HEAT

1. Regulation of Body Temperature

The human body is adjusted to work best at a certain temperature, which is called the normal Any variations from it are detrimental to the proper working of the organism Provision is therefore made in the body to regulate the temperature and keep it at the required level In the cold blooded or poikilothermic animals, the temperature depends on the surroundings It rises *in hot weather and falls in the cold and the life of the animal varies accordingly In the warm blooded* or *homo thermic animals*, the temperature is maintained at a constant level independently of their surroundings Transitional forms between these two types occur such as in hibernating animals The mean body *temperature maintained by warm blooded animals differs in different animals e g*, among the birds it usually lies between 40°C (104°F) to 43°C (107 6°F) or more In most mammals, the mean body temperature is lower than birds' but somewhat higher than that of man

Normal variations also occur in the body temperature in human beings The normal temperature in man is usually taken to be 37°C or 98.4°F but it is well known that the temperature differs in different parts of the body and also at different times of the day The rectal temperature is nearly 0.6°C or 1 0°F higher than the mouth temperature, the temperature in the axilla is 0 6°C or 1 0°F lower than the mouth temperature. As regards the diurnal variations the temperature rises during the day and attains its maximum late in the afternoon (37 5°C at 6 p m) it falls during the night and reaches its minimum in the early hours of the morning (36 2°C at 4 a.m) The difference in the maximal and minimal temperature usually amounts to somewhat over 1 0°C or 1 7°F The cause of these variations is not clearly understood but is attributed by some to muscular activities during the day and rest during the night Food has also something to do with it as diurnal variations of temperature are not so marked during starvation The temperature also varies at different periods of life The temperature in the infant is higher than in later life The body temperature rises several degree after exercise (1 to 4°F per rectum but oral temperature may remain the same) Temperature after exercise takes 30 to 60 minutes to return to normal

Apart from the small diurnal variations the temperature of the body is maintained at a remarkably constant level by the physiological processes in the body This is *accomplished by a fine adjustment of heat production* and heat loss. Any change in the environment which involves a marked increase or decrease of temperature quickly brings the heat regulating mechanism into action The temperature of a normal person rises when muscular work is undertaken A brisk walk for two hours may raise the rectal

Heat production is governed by (1) The motor nerve centres and motor nerves to muscles and glands (2) The quantity and quality of the food consumed The heat generated depends on the amount of food oxidised and the activity of glands and muscles Th a starving animal shows a lower temperature than one fed normally *Although* ... has been shown ... rare, a high ... heat in these ... *Metabolism* ... e glands are

The *heat produced depends upon* the basal body metabolism and upon excesses above this resulting from muscular activity and the ingestion of food. The basal metabolic rate (B M R) of an individual means the production of heat with the body at complete

muscular repose and fasting The rate is subject to marked physiological fluctuation According to Benedict the average basal metabolism of a normal adult is about 25 calories per kilo of body weight per day The B M R is usually calculated in calories per sq. meter of body surface. If height and weight of an individual are known, his body surface can be calculated from [illegible]
meter of body surface per hour L[illegible]
metabolism than heavier ones, usually [illegible]
The heat production is increased by [illegible]
man of sedentary habit produce abo[illegible]
produces as much as 6,000 calories per day.

Heat loss

[illegible]
1 on [illegible]
tions [illegible]
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tion [illegible]
evap[illegible]
by th[illegible]
resul[illegible]
of blood vessels is brought about by the vasomotor centre in the medulla which ensures that the blood supplied to the vital organs is maintained at a proper temperature The constriction will lessen the amount of blood circulating through the skin vessels and thus reduce the heat loss through the skin. Shivering will increase heat production and by diminishing heat loss and increased heat production the effects of sudden cooling will be counteracted Increase in the surrounding temperature will on the other hand involve the reverse kind of reaction by the same heat regulating mechanism There will be a dilatation of the skin vessels and increased perspiration. Both these factors will prevent the body temperature from rising above the normal by increasing the heat loss from the body The temperature is thus kept constant by changes in the production and dissipation of heat.

Heat loss from the body usually amounts to 70 per cent from radiation convection and conduction, 14.5 per cent from evaporation of sweat, 8.0 per cent from vapourization of water from the lungs and about 7.0 per cent from other sources

The delicate adjustment of heat production and heat elimination is under the control of the central nervous system The principal centres concerned in heat regulation lie near the basal ganglia and control both the production and the dissipation of heat They in their turn are influenced by afferent stimuli from the skin and mucous membranes as well as by the temperature of the blood which circulates through them, and they work in close co-operation with the vasomotor respiratory and the sweat centres.

Regulation against over heating

If the amount of heat generated is greater than that eliminated a rise of body temperature is the result. Production of heat is increased after food and especially after protein food, but this increase is never great and is promptly eliminated Overeating especially by consumption of meats may increase discomfort during hot weather by throwing an extra burden upon heat elimination, but this rarely causes any appreciable rise Muscular activity, on the other hand is one of the important causes of over heating It has been seen that during moderate exercise the total metabolism of the body may be increased 2 to 3 times and after violent [illegible]
With the increase in metabolism the [illegible]
to see an increase of 2° to 3°F in [illegible]
maintained by increased dissipation, b[illegible]
of the body and by deep breathing. [illegible]
of temperature may occur and heat stroke may result. This phenomenon is very well illustrated in the case of certain animals like the dog in which perspiration is almost absent If evaporation from the tongue is prevented in such an animal, by making him breathe through a tracheotomy cannula and the animal is made to take exercise, the temperature rises so high, following a brief period of muscular exercise, that the animal may die of heat stroke In man [illegible]

the temperature of the blood coming to them and (2) by reflexes from the skin In man reflexes from the skin play a very important part The rate of evaporation depends on the humidity of air Movements of the air assist *in evaporation from the skin and* excessive heat is borne better when the air is in motion In tropical climates where the external temperature is high the increased dissipation keeps the temperature down at the same time the individual feels relaxed restricts his exercise and food and thus helps in diminishing heat production

Man can tolerate a much greater range of low temperature protection against heat loss being assisted by a thick layer of fat under the skin which is a bad conductor of heat. In animals fur and other covering and in man clothes prevent dissipation Besides this, *two other factors are important (1) Physical regulation i e, by constriction* of *cutaneous* vessels so that less blood flows through the periphery Even exposure to moderate cold reduces the cutaneous supply of blood of the arm to one half or less of what it is at a comfortable temperature (2) Chemical regulation i e by increased metabolism in the muscles as shown by shivering This only comes into force when the physical regulation does not suffice After division of the dorsal cord the metabolism fails to show the characteristic c ... paralysis of muscles. Extra heat is ... f over heating the mechanism is ... y sensory impulses from the skin ... of the cutaneous vessels of the ... ise of temperature by increased r ... essels

2. *Pyrexia and its Treatment*

Fever is derived from Latin word *febris* meaning to boil It is a complex phenomenon the main feature of which is a rise of the body temperature associated with disturbance *of metabolism special senses pulse respiration etc The rise in temperature in fever* is due to a defect in the heat regulating mechanism which is not clearly understood. Physiological fever we have already seen is produced by immersion in a warm bath at 40°C and is not accompanied by any of the other phenomena of fever above described. *Entrance of living or dead bacteria or their products in the blood or protozoal* organisms produces fever No constant relation exists between the severity of infection and the height of fever The cause of marked fluctuations in temperature during infections is not understood. In some it is merely an exaggeration of nomral diurnal variations Other conditions giving rise to fever are injection of foreign proteins destruction of cells ... umber of chemical ... caffeine cocaine ... other substances ... the brain in the ... h constriction of ... the body mainly ... general way the ... and undoubted ... planation is that ... e heat regulation ... urs after cerebral ... ical irritation of the basal portions of the brain Injection of water also produces a ... e of temperature, the cause of *the so called water fever probably being the presence of minute traces of* organic matter (pyrogens) in the water used for injection Excessive loss of water may lead to elevation of body temperature

With sweating there is a considerable loss of salt It has been shown that the ratio of potassium to sodium in the sweat is greater than in the plasma and after an exposure to tropical conditions a definite fall in the potassium concentration of the plasma occurs

The dangers of excessively *warm conditions are twofold The first is the danger* of collapse from diminution of the distension of the circulation resulting partly from a dilatation of the circulatory bed and partly from a loss of fluid into the intercellular spaces and through the sweat The second danger is that an excessive loss of K chang *ing the ratio* of Na K may be the cause of hyperpyrexia as a result of which the temperature continues to be maintained at a dangerously high level or to mount still higher even after removal of initial cause There are, of course conditions so severe that no device will prevent a fatal rise in temperature but below this impossible level the danger of

failure of the circulation may be avoided by an adequate supply of sodium chloride and water, and danger of hyperpyrexia by an adequate supply or reserve of potassium The advantage of the first is confirmed by a wide range of practical experience, the second is, it should be emphasized, speculative

Heat regulator in fever

Fever may be continuous, remittent and intermittent The temperature may fall by lysis or crisis The febrile temperature is primarily due not to an increase in the heat production or to an absolute inefficiency in heat dissipation but to a lack of adjustment between the two The heat regulation in fever behaves as if the regulatory centres were set to maintain the body temperature at a new level which is maintained in the same way as normal temperature. In fever the heat regulation is less perfectly adjusted than in health as it is much more difficult to reduce the temperature of a healthy man than a fevered individual either with cold baths or with antipyretic drugs The extra heat produced within the body is also less perfectly eliminated

Metabolism in fever

Metabolism is accelerated in fever as warmed tissues metabolise more material than cooled tissues, but in addition to this there is probably a toxic element that causes tissue destruction and the rapidity of protein consumption varies in different infections This increased metabolism rarely exceeds 40 or 50 per cent over normal No strict parallelism exists between the rate [illegible] he temperature The amount of protein lost [illegible] ch as 200 to 500 gm of muscle tissue per d[illegible] eins of the body are lost in the course of [illegible] ation of fever there is a marked increase [illegible] equilibrium can be maintained in fevers and the patient's strength conserved by giving adequate diet but unfortunately in many fevers the toxins produce loss of appetite which prevents intake of food and a decrease in absorption may occur The partial starvation thus produced increases protein metabolism, besides high temperature it produces further rapid wasting of tissues To supply this need administration of glucose and other similar foods is necessary

Acidosis in fever

Acidosis also occurs in fever but its occurrence is probably not as common as is supposed. Ketonuria which often occurs in febrile conditions is an indication of disturbance in fat metabolism, but is not considered as evidence of acidosis.

It is well known that excretion of chlorides in fever is decreased This is certainly true of pneumonia and other infectious diseases The retention of salt is associated with simultaneous retention of water especially in long continued fever such as typhoid the tissues therefore, become relatively rich in fluids and poor in solids A normal individual will excrete up to three litres of water which may be introduced into his body the fever patients do not do this and retain a considerable amount The extra water is however, stored mainly in the tissues and less in the blood and the same is the case with the chlorides The state of affairs is therefore different from what occurs in nephritis where the concentration of the salt is high in the blood It has been shown that antipyretic drugs bring about a dilution of the blood which favours dissipation of heat by radiation

Effects of fever

Cloudy swelling

Heat above normal body temperature especially if continued for a long time causes degenerative changes in the tissues The cells undergo cloudy swelling The proteins of the muscles coagulate at 104°F (40°C) and in nearly all tissues globulin coagulates at 45°C., mammalian muscle passes into rigor between 45° to 50°C Coagulation takes place at a lower temperature when continued for a long time Even if coagulation is not visible a change analogous to it may cause death of the cells It is possible that heat and toxin may act in a synergistic manner to disturb the functions of the cells

Pulse rate

The heat also acts directly on the heart muscle and stimulation of the nerve centres controlling the heart produces slowing or acceleration. When temperature is the only factor a rise of temperature e g 97.8° to 104°F (37° to 40°C) will cause an increase of pulse rate In addition to this, toxins play a part e g in typhoid fever the pulse is relatively slow being about 70 to 80 beats per minute with a temperature of 103° to 104°F. In scarlet fever the pulse is surprisingly rapid.

As regards the central nervous system, the toxins and other pyretics are said to produce a stimulation of the regulatory mechanism A number of drugs e.g., cocaine,

which stimulate the para sympathetic system, and cause myosis slow pulse and psychic depression, do not increase the temperature

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The practical question involved in the treatment of *infectious diseases is to what* extent should one attempt to reduce the temperature It was thought that the febrile rise of temperature was on the whole a favourable manifestation and helped the organism in overcoming infection Clinical experience shows that when bacterial infections are unaccompanied by fever they run a very unfavourable course Leprosy tuberculosis and parasitic diseases not marked by febrile reactions are usually difficult to cure and do not confer immunity Treatment of neurosyphilis by artificial infection with malaria probably chiefly acts by increase of temperature. Collapse may occur in certain conditions if the stimulus of high temperature is removed. It has been shown that with most bacteria the optimum temperature for development is confined within very narrow limits, which are exceeded by the temperature of fever The tendency of fever may, therefore, be useful but unfortunately the cells of the organism are not adjusted to work under high temperature and it may be more detrimental to them than to the bacteria. It has been advocated by some that fever is the essential manifestation of infection, that it is dangerous in itself, and should be vigorously combated The question still remains unsettled as patients with a high temperature are more sick than those with a low temperature, but this is not due to the temperature but because such patients are suffering from more severe infections. Besides this, in the most unfavourable of all infections the temperature may be low From a comparison of clinical cases it is, therefore, not possible to judge the favourable and unfavourable effects of temperature The antipyretic measures also do not give any clear answer, because not only do they reduce the temperature but they have various effects on other parts of the body, especially the brain and the circulation

Many experimental studies have been carried out in this connection Rabbits have been kept with a body temperature of 41°C (105 8°F) and over for weeks at a time without any serious damage The degeneration of internal organs observed in infectious fever is probably not due to prolonged overheating of the body Serious effects are only produced [illegible] fevers The damage a [illegible] ise of temperature [illegible] n? The high temp[illegible] lp the host in developing protective mechanisms. The temperatures encountered in certain fevers are sufficiently high to inhibit the growth of certain bacteria Pneumococcus and gonococcus do not grow well at a temperature of 104°F (40°C.) or over *Moderately* high temperature even though maintained for a long time, is not in itself a dangerous manifestation In artificial infections in animals an increased temperature has a favourable effect on the course of the infection and increases the speed with which the protective anti bodies are formed In the treatment of fevers therefore one should not try to bring down a high temperature too vigorously unless it is above 105 8°F (41°C) In such cases the reduction of temperature is comparative but in ordinary febrile temperatures there is no need for active interference The value of antipyretic measures in such cases is to be judged not solely from their effect in reducing the temperature but also from their effect on the general condition of the patients and especially on their nervous system and circulation

The temperature of the body can be lowered by factors which decrease the production of heat or increase its loss As the temperature tends to fall below normal compensatory reactions are at once set up to keep the temperature normal. It is not found possible to depress the temperature without effecting profound changes On the other hand, it is relatively easy to lower an abnormally high temperature because it coincides with the natural tendency to return to the normal or physiological state Antipyretics therefore have no effect on normal temperature but readily act when pyrexia is present Antipyretic measures can be divided in three main groups —

(1) Those that abstract heat *e g* application of cold in form of baths sponging packs This subject has been discussed under physiotherapy

(2) Those that increase the dissipation of heat by dilating the cutaneous vessels and by restoring the water content of the blood Their action is mainly central These are antipyretics of the coal tar group *e g* acetanilide phenazone (antipyrin) phenacetin

(3) The cinchona alkaloids especially quinine which is said to diminish heat production. Salicylates aconite and veratrum probably diminish heat production by slowing the circulation

3 Antipyretic and Analgesic Drugs

Antipyretic drugs

High temperature in the old days was chiefly combated by baths and giving such vegetable alkaloids as aconite and quinine It was discovered as early as 1875 that salicylic acid and related bodies produce a fall of temperature in fever Most of the modern antipyretics were discovered in an attempt to synthesise quinine A large number of bodies were introduced but those of importance are acetanilide phenazone phenacetin and amidopyrin or pyramidon These are all benzol derivatives and prepared from aniline Phenol guaiacol salicylates and many other compounds also lower febrile temperature but they are much inferior All these drugs have the same action The antipyretic drugs are divided into three groups —

(1) The essentially antipyretic drugs are (*a*) acetanilide and acetophenetidin or phenacetin and (*b*) antipyrin and amidopyrin also known as pyramidon, they are also analgesic Like alkaloids these are precipitated by tannic acid alkalies and other alkaloidal precipitants

(2) The anti rheumatic group consists of salicylic acid and its derivatives such as acetylsalicylic acid (aspirin) etc Cinchophen or atophan also comes under this group

(3) The antimalarial antipyretics, *i e* the cinchona alkaloids

Phenacetin

Acetophenetidin or phenacetin Phenacetin is a white crystalline powder The dose is 5 to 10 grains (0 3 to 0 6 gm) It is much less toxic than acetanilide It produces a feeling of ...

... amino phenol and ... the body

Antipyrin

Antipyrin or phenazone It is derived from phenyl hydrazone the dose is 5 to 7 grains or more (0 3 to 0 5 gm) and its action is very similar to acetanilide

Amidopyrin

Amidopyrin or pyramidon is a derivative of antipyrine It is given in doses of 5 grains (0 3 gm)

These drugs have no effect on the normal temperature Antipyrine is more analgesic in neuralgic pains and neuritis originating from the spinal cord than acetanilide and is therefore largely used in the shooting pains of tabes which it may not always relieve Phenacetin is used more for headaches Phenazone is slightly less toxic than acetanilide and little more ...
put on the ma...
the circulation ...
It is not very
erysipelas and ...

Cryogenin

Cryogenin occurs in crystalline masses and is slightly soluble in water It has been used as an antipyretic to control high temperature, and this is found valuable in the treatment of phthisis and lingering pyrexia that sometimes follows the acute stages of an infection The dose is 3 to 24 grains but it should not generally exceed 10 to 15 grains daily

Salicylates

Salicylates These compounds lower the febrile temperature promptly The mode of reduction is very much like that of the members of the coal tar group *i e* increased loss of heat by dilatation of cutaneous vessels and increased perspiration In healthy individuals this is compensated for by increased heat production so that the normal temperature remains unaffected Salicylates may easily take the place of other antipyretics and are probably safer but may produce unpleasant side effects Small doses of acetylsalicylic acid or aspirin (5 to 10 grains) are commonly used in mild fevers and not only reduce temperature but also remove unpleasant symptoms such as headache Novaspirin (methylene-citrilsalicylic) has no advantage

In 1937 the citizens of the United States consumed 5 143 672 lb of aspirin This works out at 48 five-grain tablets per head of population. This shows the popularity of this drug After taking aspirin patients often complain of heart burn and epigastric discomfort presumably because of liberation of a small quantity of salicylic acid in the stomach by the gastric acid Aspirin lying on the mucous membrane of the stomach may produce irritation resulting in local hyperaemia and even submucous haemorrhage If taken after

food or with milk it probably has no deleterious effect. Calcium aspirin (which is much more soluble than ordinary aspirin) causes only slight gastric irritation, and is recommended

Various constitutional upsets have also been attributed to aspirin from time to time. Aspirin hypersensitiveness is the most common form of drug allergy and in sensitive subjects *e g* asthmatics with nasal polyps and people who have *a family history of allergy* special caution is indicated. The potential dangers of almost any drug are such that we should not be unduly impressed by rare untoward reactions and it is not surprising that an allergist should be emphatic about the ill effects of some drugs that the general practitioner regards as eminently safe. Dangerous reactions may occur in sensitive persons but these occur rarely

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Cinchophen or atophan is phenylcinchoninic acid. It has a biting bitterish taste and is irritating to the stomach. It has a pronounced action on the liver cells and increases the quantity of bile. Its absorption from the intestine is irregular and uncertain, and some can be recovered from the urine. Cinchophen is an antipyretic but its chief action is an analgesic in rheumatism and as a mobilizer of uric acid. The dose is 5 to 15 grains (0·3 to 1·0 gm)

Neo-cinchophen is an ethyl ester. It is also called novatophan and tolysin. It is tasteless and does not irritate the stomach. It has also a cholagogue action and has less destructive effect on the liver cells than cinchophen. The dose is 8 to 15 grains
Both these compounds are chiefly used in rheumatism and gout

The antipyretic action of quinine has been dealt with in another section. In malaria, quinine reduces the temperature because of its effect on the malarial parasites, but in addition it has a general antipyretic effect in fevers other than malaria. Large doses of quinine are said to depress the metabolism by 10 per cent the heat loss appears to be but little altered. Quinine has also a sedative action on the centres though it is not so marked as with other antipyretics. Quinine however conserves energy probably by decreasing metabolism instead of increasing the heat loss. In such diseases as influenza when the depressant action of the aniline drug is undesirable quinine is very useful. The antipyretic dose is 5 to 15 grains

In normal persons even large doses of these drugs produce no effect. In fever a fall is produced beginning within 2 hours and lasting for 2 to 4 hours. The fall is accompanied by profuse perspiration due to dilatation of cutaneous vessels and increased heat loss owing to direct action of the drug on the heat regulating centres. The effect of direct application of these drugs to the region of the heat centres was studied both the antipyretics and narcotics produced a fall. Central nerve stimulants such as caffeine produced a rise. The mechanism of rise of temperature is a stimulation of these centres and the antipyretics therefore act by depressing them

Some individuals show an idiosyncracy to these drugs cyanosis and collapse being produced with ordinary therapeutic doses. Papular and erythematous skin rashes may follow phenazone and acetanilide antipyrin produces a scarlatiniform rash with œdema of the face and fever. It may also produce urticaria, or a vesicular bullous or eczematous eruption. A large number of [illegible]
from their use the chief
and irregular pulse dyspnœ
5 grains (0·3 gm.) but reco
often follow from 0·2 to 1·0 gm doses. Antipyrin may cause burning and swelling of the whole alimentary tract with nausea vomiting diarrhœa, skin rashes mental dullness tremors cerebral convulsions coma and death from failure of respiration. In the case of amidopyrin excitement increased reflexes and a measles like eruption have been noticed. Frequent use of the drug may produce agranulocytosis

Acetanilide and phenacetin produce acute and chronic poisoning in one form collapse and cardiac failure being prominent features and in the other cyanosis accompanied by anæmia emaciation and weakness. There is dyspnœa and the heart is rapid and weak. The cyanosis is said to be due to the formation of methæmoglobin, but it is probably produced by para amidophenol or some other aniline derivative which has been found in the blood and urine sulphæmoglobinæmia is said to be present. Methæmoglobin has, however been seen spectroscopically. Cyanosis may persist for weeks after the drugs are stopped. Caffeine is often combined with these drugs to prevent depression but it is said to increase the toxicity of acetanilide. Sodium bicarbonate is believed to lower their toxicity

Treatment consists in washing out the stomach with alkaline solution, maintenance of body temperature and combating the collapse with atropine caffeine strychnine digitalis etc Chronic poisoning is met with the symptoms being cyanosis anæmia disturbance of digestion headache dyspnœa on exertion weak pulse extreme muscular weakness

Habit formation

Habit with these drugs is formed by nervous patients suffering from headache neuralgia, etc The habitues show mental depression digestive disturbances anæmia and general weakness The habit is not vicious like the morphine habit but it may be difficult to break

4 Treatment of Fever

From the foregoing discussion it is obvious that pyrexia alone does not constitute the sole indication for treatment The toxic state of the patient is a more important factor When it is desired to reduce temperature it is advisable to control it by use of cold sponging or bathing Antipyretic drugs should be resorted to as little as possible The objection to these is that they depress the patient and decrease his power of resisting disease

Fluids

In all fevers especially when they are prolonged water should be freely given whether the patient asks for it or not Not less than two quarts should be given to an adult daily It is not only essential to flush the kidneys and remove toxins circulating in the blood but it is essential for the proper functioning of the body The turnover of the fluid during digestion has been estimated at five quarts per day of which no less than one quart is bile the fluid being excreted and reabsorbed Considerable quantities of water are lost in the urine and respiration and a certain amount in normal stools In heat elimination an important factor is the distribution of water in the body By dehydrating a dog a high temperature may be produced The fever is caused by blood concentration and checked by blood dilution In influenza typhoid pneumonia salt fever, inanition fever and other fevers the blood has been [illegible] of the tissue colloids [illegible] viscosity is increased [illegible] is diminished sweat [illegible] er The dilution of the blood by increased ingestion of fluids remedies these defects increases heat elimination and lowers temperature Antipyretic drugs such as sodium salicylate aspirin and cinchophen are said to act in fever by lessening the blood concentration and thus increasing heat elimination In non febrile patients in whom there is no dehydration there is no fall of temperature in equivalent doses

Analgesics in the treatment of fever

The ch[illegible] condition [illegible] system [illegible] ache and [illegible] system ar[illegible] tion of temperature is of course essential in case of sunstroke for if this is not done the temperature rises steadily till the patient dies Such cases can only be treated by cold sponging or cold baths There is general agreement that antipyretic drugs are of little value in the treatment of severe fever when the temperature is retained at a high level for many weeks Such cases are benefited by cold sponging or cold baths Even if the bath may not produce a prolonged lowering of the temperature the short fall gives the organs of the body rest and the results are very satisfactory The chief use of antipyretic drugs is in mild cases of fever and in these they generally make the patients more comfortable and often assist in producing sleep though they may not

influence the course of the disease. They neither strike at the cause of the fever nor at any symptoms other than those resulting from hyperpyrexia They make the type of disease neither less severe nor shorter For instance in malaria, antipyretics may prevent the development of the paroxysm but they do not attack the cause of the disease They are merely a symptomatic and not a specific mode of treatment and symptomatic treatment should always be carried out with care, as more harm than good may be done When it is not possible to attack the cause of the disease it is advisable to remove the objection able symptoms This they do by their sedative action on the pathologically stimulated centres and on the sensory part of the cerebral cortex Schmidberg gave them the name of "fever narcotics' and this is a very suitable name, as now-a days they are seldom employed to combat hyperpyrexia, but rather in hope that the patient will be benefited by their sedative action on the symptoms of fever due to hyper excitability of the brain centres They decrease pain in the limbs headache delirium, and restlessness, clear confusion of mind and induce sleep The effects of these drugs vary with the individuals, some people can take large quantities without effect, while others are affected by small quantities

When antipyretic drugs are used, it is better to give a small dose before resorting to a large dose Special care is taken when these are given in diseases where the temperature falls by crisis as a dose before the crisis may produce dangerous collapse by exaggerating the physiological fall

In cases of pain and discomfort without fever, such as headache, migraine neuralgia muscular rheumatism, pains of locomotor ataxia dysmenorrhœa and in various nervous conditions in chorea whooping cough, diabetes insipidus antipyretic drugs especially acetyl salcylic acid (aspirin) generally give relief Pyramidon is said to be a specific for measles The drugs are usually given in the form of capsules or tablets for internal use and are sometimes combined with codeine bromides, etc, if necessary On account of their depressent action on the heart these drugs are often combined with cardiac tonics such as caffeine and digitalis

Is fever produced by diathermy and physical means the same as fever occurring from infections The answer is in the negative. From the strictly physiological standpoint, the majority of evidence points towards the two being entirely different with the exception of temperature or heat which they both share in common. There are some findings for example, in the urine and sweat which are similar and the clinical interpretation of conditions and results add further to this conception. There is a marked increase in basal metabolism in artificial fever and possibly much of the benefit comes solely through this source since its application is nearly always in diseases which at that time are not running temperatures of their own accord Possibly the increased metabolism and circulation alone hastening absorption and elimination of their by products can be just as important a factors From the physiological point of view hyperpyrexia produced by physical means is not synonymous with spontaneous fever produced by disease. Hyperpyrexia induced by malaria, chemicals foreign proteins, etc. is also different from that produced by physical means The role played by heat retention in combating disease might share a common denominator in all three types of fever The heart rate is subject to changes in skin temperature more definitely than to changes in body temperature

5. Effects of Heat (Heat Stroke)

If heat loss is prevented the body temperature rises, *e g*, if a normal man is immersed in a hot bath up to the neck the body temperature rapidly rises from 37°C to 38°C (98 4°F to 100 4°F) or to 40°C (104°F) or even higher, according to the temperature of the bath This is what sometimes happens in those living in hot climates and heat stroke is the result The most common form of heat stroke is what is commonly known as 'a touch of the sun.'

The milder cases are termed heat exhaustion It follows generally after an individual has been exposed to the sun and glare There are three forms (1) Mild form The patient suddenly becomes acutely sensitive to heat and feels weak there may be nausea headache dizziness staggering pain in the limbs thirst and sleeplessness The temperature may or may not rise He may either collapse in the sun or may drag himself into the shade before collapsing The pulse is at first rapid and weak the skin is clammy the respirations are shallow and hurried the pupils are dilated and the temperature is normal or subnormal The mortality in this type is very low but the patients often recover slowly

Mild form.

(2) Severe form In this form the temperature is considerably or ex tremely elevated This is frequently fatal

(3) Heat cramps —Here cramps of muscles occur

(1) Hyperpyrexia

The symptoms start as in the mild form but consciousness is lost early the skin becomes dry and hot and the temperature rises very rapidly The pupils are dilated the pulse becomes rapid and full and the breathing is deep at first but later shallow and finally of the Cheyne-Stokes type the pupils become con tracted and the conjunctiva injected The urine and stools may be passed involuntarily there may be muscular twitchings and rocking of the head Epilepti form convulsions may occur and death follow The sudden onset is usually preceeded by a 48 hour period of non sweating

The temperature usually is between 99 1° to 104 7°F (37 3° to 40 4°C) In severe forms the body temperature rises rapidly from 104° to 111.2°F (40° to 44°C) rarely to 114 8°F (46°C.) If the temperature does not rise beyond 111 2°F (44°C) recovery is possible under vigorous hydrotherapeutic treatment When the temperature exceeds this limit recovery is rare the patient as a rule

viduals whose regulating mechanism against excessive heat is less perfect Alcohol is an important predisposing factor because it lessens the effectiveness of the regulating mechanism by depressing the heat regulating centres and paralys ing the cutaneous vessels When the patient s temperature is brought down by vigorous hydrotherapeutic measures he may show continuous fever for days or even weeks after the acute hyperpyrexia has subsided During this time the body temperature is extremely sensitive to external influences and for years afterwards these patients may show increased sensitiveness to heat All these factors show that heat stroke is usually associated with and is followed by a marked disturbance in the heat regulation of the body the centres which regulate the heat loss being deranged

Heat prostrat

Power of acclimatization to heat differs in different individuals Persons with organic disease of heart and kidneys and such conditions as hyperthyroidism ichthyosis etc stand heat badly and should avoid exposure to it In people coming from temperate climates physiological adjustment takes place in 2 or 3 weeks Hours of work should be so adjusted that least physical exertion is done in the hotest part of the day Sedentary workers should take exercise during cool hours and rest during hot hours of the day Starches and sugars which

Prophylaxis

are heat producers should be restricted Alcoholic beverages should be forbidden till sundown Water and salts should be freely taken In labourers who sweat freely two teaspoonful of salts with plenty of water should be taken and in sedentary workers one teaspoonful daily

Clothing should be light and loose and of porous material this promotes absorption of sweat and favours evaporation of sweat If worn in the sun, it should be white or light in colour Helmets should be worn to protect the head from the sun rays Air conditioning prevents acute heat effects and adds to comfort

Ultra violet rays of the sun are not so important as the longer heat rays which have great penetrating power

In mild cases if the patient is put in a cool place and is given drinks of cold water he often improves If the pulse remains weak give a diffusible stimulant such as half a drachm each of aromatic spirits of ammonia and spirits of ether or an injection of camphor in oil Sometimes in these cases the temperature falls to much below normal and it is necessary to apply heat to the body and hot drinks have to be given The patient should be carefully watched as a sudden rise of temperature may occur

[illegible] of ammonia
caffe [illegible]
made [illegible]
patie [illegible]
rectal temperature falls to 102°F (38 8°C) When this temperature is reached the body will probably continue to lose heat in favourable cases after removal from the bath even sometimes to below normal While the patient is in the bath his body should be vigorously rubbed because unless hyperæmia of the skin is produced by this procedure the overheated blood will be driven to the internal organs by the contraction of the blood vessels Rubbing the body with ice or placing the patient in a sheet wrung out of iced water are less efficient than the bath If possible put patient in an air conditioned room at temperature of 65°F with low humidity If plethora and high blood pressure remove 200 to 500 ccm of blood by venesection

An enema of 2 or 3 pints of ice cold water is often very useful When ice is not available the heat should be abstracted from the body by evaporation of water This is done by spraying water from a fine nozzle on to the stripped surface of the body a current of air being maintained by hand or electric fans Equally good results are obtained by wrapping the patient in a sheet wrung out in water and putting him under a fan Tepid water by this method will remove as much heat as ice cold water This method is very effective and is now extensively used in hospitals When the rectal temperature (it should be frequently taken) has reached 102°F (38 8°C) the evaporation is stopped Cessation of sweating is a sign of impending recurrence Such patients should at once be covered with a moist sheet and put under a fan Once the artificial perspiration is established recurrence is often averted To combat dehydration give fluids freely Intravenous injection of salt solution with 5 per cent glucose are beneficial When cramps are present give salt solution freely Light chloroform anaesthesia may be used to control convulsions Lumbar puncture may be necessary if cerebro spinal fluid pressure is increased If malaria is suspected injections of quinine should be given Morphine should not be used

(2) Heat Exhaustion

Symptoms

Heat exhaustion is also known as heat prostration or heat syncope In this condition there is little if any rise of temperature Predisposing factors are fatigue alcoholism debilitating diseases chronic circulatory disorders etc Symptoms develop rap dly or even suddenly There is nausea giddiness weak ness inability to stand or walk the blood pressure is low pulse small weak and rapid pupils dilated and skin moist

Mild cases react well to rest alone but death may occur from failure of circulation the condition resembling shock Prognosis is favourable if diseases of heart and kidney are not present It is frequently the cause of death in the old and debilitated

Treatment

The patient should be put in recumbant position in a cool place with free circulation of air If temperature is sub normal wrap in blankets and apply hot water bottles to feet Cold water containing 1 3 gm (20 grs) of sodium chloride in a quart of water to be given Hot tea or coffee or aromatic spirit of ammonia may be given Strychnine by injection is useless Digitalin may be given but morphia is contraindicated

(3) Heat Cramps

Heat cramps also known as fireman s cramps stokers cramps and miners cramps

This is the type of heat exhaustion seen frequently in labourers working in engine rooms or in deep mines where the temperature is high The patient gets muscular twitchings for a time and is then siezed with violent painful cramps principally of the abdominal muscles The spasm may involve other muscles and may become so general as to resemble an epileptic attack. Other symptoms are nausea dizziness and stupor the patient being usually pale and perspiring The pulse is rapid but strong and the temperature only slightly above normal The condition is believed to be due to loss of chlorides to below normal by ex cessive ingestion and excretion of water

Prophylaxis

Good health should be maintained with nutritious diet and adequate rest Workmen srould be provided with abundant supply of drinking water and one gram tablets of sodium chloride Concentrations of 0 1 to 0 15 per cent in drinking water are recommended as when taken cool such water has no saline taste and quenches thirst Stronger solutions increase thirst Stokers in ships often take sea water and miners in England add salts to their beer for this purpose New workers should be specially protected in the beginning and physical exertion gradually increased

Treatment

This consists in rest and restoration of sodium chloride content of the serum to the normal level This is best attained by intravenous injection of normal saline to which sodium bicarbonate or glucose may be added Half to one litres may be given during the first six hours and repeated if necessary Usually cramps stop after the first injection Injections are given till the patient can take salt by mouth in form of tablets or normal salt solutions Dose of salt is one tablet (1 0 gm. each) every houg during day time till 15 tablets are given Sufficient fluid should be given to compensate for loss by sweat.

In addition to the various causes of hyperpyrexia already mentioned there may be certain other types of fevers, the etiology of which is imperfectly understood Low persistent fever or an evening rise of temperature may occur in tropical climates, in persons who are run down or have recently suffered from a prolonged attack of fever This is probably due to the heat centres not acting effectively and can be controlled by sending the patients to a cool climate such as a hill station

(4) Prickly Heat

(See under skin diseases) It is a superficial dermatitis in which there is cystic dilatation of sweat gland ducts due to occlusion of their openings It *is associated with high and humid temperature and is accompanied by itching* and burning It is commoner in the obese or stout individuals It is severe in debilitated and weak individuals There is acute superficial inflamation of the sweat follicles which may become confluent Secondary bacterial infection may occur The condition may last througrout the damp season in the tropics Keep the skin as dry as possible with dusting powders Avoid tight underclothing

CHAPTER VIII

DIET AND DIETETICS IN THE TROPICS

FOOD AND ITS CONSTITUENTS AMOUNT OF FOOD REQUIRED IN HEALTH MINERAL CONSTITUENTS WATER DIETETIC SOURCES OF THE MINERAL CONSTITUENTS—THE INDIAN DIETARY MILK PRESERVES—ADAPTATION OF DIET IN TROPICS—DIETETIC ERRORS IN TROPICS ALCOHOL, DIETETIC ERRORS OF INDIGENOUS RACES—DIET IN THE TROPICS DIET IN DISEASE, DIET IN PREGNANCY AND LACTATION, DIET IN INFANCY AND CHILDHOOD INVALID DIET IN TROPICS—DEXTROSE (GLUCOSE) PHYSIOLOGICAL CONSIDERATIONS MODES OF ADMINISTRATION, GLUCOSE (DEXTROSE) IN THERAPY

The importance that the Indian patient attaches to his diet is not fully appreciated by Western practitioners The Hakims and Kavirajes lay great stress on the subject of diet In Susruta, the well known book on Hindu medicine, it is said, 'The physician that does not know the principles of dietetics cannot cure disease' This idea is ingrained in the minds of Indian patients and unless proper attention is paid to this aspect, patients are not convinced about the utility of a particular line of treatment It is surprising, however, how few physicians practising Western medicine pay any special attention to this important subject We have, therefore, thought it necessary to give a chapter on this important subject

1. Food and its Constituents

Food is essential for the maintenance of the body processes The human body can be compared to a machine, the fuel for which is supplied by the food that we take every day Food provides the materials for growth and repair of the fabric of the body It supplies materials which can be oxidised in the body, with the result that the energy set free by oxidation may be used in performing work and in producing heat It also supplies the body with substances (catalysts, food hormones, vitamins) which though present in almost inconceivably minute amounts, control body function Food, therefore, is responsible for the conservation of the material of the body, the maintenance of its output of energy and for the regulation of its functions

Nutritive constituents

On chemical analysis all foods resolve themselves into the following proximate principles usually known as the 'nutritive constituents

1 Proteins, *e g*, albumin myosin gluten, legumin, gelatin
2 Carbohydrates *e g*, sugar, starch dextrin glycogen cellulose
3 Fats, *e g*, suet lard olive oil, butter fat.
4 Mineral matters *e g* common salts and compounds of calcium iron iodine potassium magnesium
5 Extractives and flavouring materials
6 Vitamins
7 Water

Functions of food

The various functions of food are fulfilled by the different groups in different measure. The first function that of building up and repairing the tissues can be ful filled by the proteins the mineral matter and the water It is true, of course that glucose one of he carbohydrates enters into the construction material of all nuclei of the mucin of mucous cells and of cartilage while substances such as lecithin with a large portion of their molecules consisting of fatty acid derived from fat, appear in every cell in the body These substances however, are almost incidental to the structure of the body which in the main consists of protein, of mineral matter and of water None of these is sufficient by itself The second function, that of serving as a source of energy, is mainly fulfilled by the fats and carbohydrates, though we have to recognise that a fair proportion of the energy output of the body may be derived from the oxidation of the proteins The third function that of regulating the processes of the body, is fulfilled

by mineral matter and by the vitamins It is known that muscles (*e g*, heart muscle) will not contract in the absence of carefully adjusted amounts of mineral matter Bone and teeth are irregularly and incompletely formed if in addition to the essential calcium and phosphorus in organic or inorganic combination there be little or none of vitamin D in the food Many other of the processes of the body depend upon the supply in the food of minute amounts of mineral matter and vitamins

Physiological opinion has undergone considerable changes during the last century with regard to the relative values of proteins carbohydrates and fats. Liebig thought that proteins were the chief producers of
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maintained without the presence in the food of protein mineral matters and water The proteins present should be complete proteins *i e*, contain within them all the essential amino acids, incomplete proteins such as gelatin cannot by themselves take the place of complete proteins in the diet

The functions and the parts played by the different proximate principles can therefore be stated in tabular form as follows—(Hutchison and Mottram) —

Tissue formers and repairers	Work and heat producers	Regulators
Complete proteins Incomplete protein in the presence of complete proteins Mineral matters Water	Complete and incomplete proteins Fats. Carbohydrates	Mineral matter Vitamins

It will be observed that the proteins appear in two categories out of three. They are thus of immense importance in the diet. A diet may be predominantly protein and yet life may be maintained thereon Without protein life is impossible as the daily wear and tear of tissue protein must be made good

From the point of view of physicians a knowledge of the composition and the nutritive values of foodstuffs in common use is of prime importance There are methods by which one can judge the relative merits of these food materials

Ordinary analysis tells how much protein fat and carbohydrate are contained in hundred grammes of the food and from this we can form an idea of the value of a particular food as a source of building material or energy

The amount of heat which a food yields on complete combustion may be taken as a measure of its value as a source of energy to the body The unit of heat production is expressed in *calorie* which is the amount of heat required to raise the temperature of 1 gramme of water through 1°C This is the small calorie For convenience in measuring the amount of heat of foodstuffs the large or kilo-calorie is used, *i e* the amount of heat required to raise 1 kilogramme (or 1 litre) of water 1°C (or 1 pound of water 40°F) The determination of the caloric value of a food therefore gives an indication as to its value as a source of energy The heat values of 1 0 gm each of the following are —

Fat	—	—	—	9 3 Calories per gm
Carbohydrate	—	—	—	4.1 Calories ,,
Protein	—	—	—	4.1 Calories ,,

It will be seen that the caloric value of fat is nearly twice that of protein and carbohydrate. The caloric value of a food therefore is greatly affected by its fat content

The following is the number of calories yielded by the complete combustion of one gramme of the various foods according to Hutchinson —bacon 8.86, butter 8 60 fat goose 4.95, fat pork, 4.12, fat mutton 4 03, rice 3 51, peas 3 31, fat beef 3.27, maize 3 7, coarse white bread 3 03, wholemeal bread, 2 78, fine white bread 2.74, cheese 2.4 eggs, 1 59, lean beef 0 98, apples 0 59, spinach, 0 34, oranges 0 33, strawberries 0 32, lettuce, 0 20.

Burroughs and Wellcome have compiled the following useful table —

COMPOSITION AND CALORIE VALUE OF PRINCIPAL FOODS

30 grammes (1 oz)	Protein Grammes	Fat Grammes	Carbohydrate Grammes	Calories
Bread	3	—	16	80
Butter	—	25	—	225
Meat (uncooked lean)	6	3	—	50
Meat (cooked, lean)	8	5	—	75
Egg (one)	6	6	—	75
Cream 20 per cent	11	6	1	60
Cheese (Cheddar)	8	10	1	125
Milk	11	1	1 5	20
Potato	1	—	6	30
Peas (dried) Beans (haricot)	7	0 5	17	100
Celery, Cabbage, Cauliflower	0 5	—	0.3	3 2
Lettuce	0 5	—	0.2	2 8
Tomatoes	0 5	—	0.7	4 8
Fish Codmhaddock (cooked)	6	—	—	25
Bacon	5	15	—	155
Oatmeal dry weight	5	2	20	120
Broth	0 7	—	—	3
Small orange or half grape fruit	—	—	10	40

Physiological test

It is not enough that food should contain a considerable proportion of protein carbo hydrate and fat and should be capable of yielding energy on oxidation It must be of such a nature that it is easily digested in the alimentary tract and absorbed more or less completely into the blood There are many substances, *e g*, saw dust agar, hoof parings which are complete foods so far as their chemical analysis and physical properties of heat production are concerned but which nevertheless are not digestible and cannot serve any useful purpose to the body mechanism, In giving opinion on the qualities of a particular food, therefore, several factors have to be taken into consideration

Digestibility

(i) *The digestibility of foods* By digestibility the biochemist means foods which are rapidly disintegrated in the body under the influence of ferments

Satiety value

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value wh [illegible] bread and green vegetables have a low one

Absorbability

(iii) Absorbability of the different constituents of various foods is another important factor in dietetics. Of the three chief nutritive constituents the proteins are the best and most completely absorbed Animal proteins (milk, eggs, meat) are much better absorbed and the nitrogen loss is much less than in the case of the vegetable proteins (carrots potatoes peas, etc.) Compared with the proteins fats are apparently very incompletely absorbed This is probably due to the fact that fat which is fluid at the *body temperature* is more easily absorbed into the blood than one which remains more or less solid The carbohydrates are more completely absorbed than any other nutritive constituent of the food Sugar probably never fails to enter the blood to the last grain and even starch only reappears in the fæces when taken in a form specially difficult of absorption, *e.g*, in green vegetables Hence foods which consist mainly of carbohydrates such as rice, leave on the whole, less solid residue in the intestine than any other

Roughage

(iv) *Roughage* Though the absorbability is an important guiding principle in the choice of foodstuffs it is not always an advantage to prescribe a diet which is completely absorbed and does not leave any residue To ensure the proper action of the bowels, the

intestines apparently seem to require a definite amount of ballast or roughage as we now popularly term it This is particularly true of herbivorous animals which, if fed upon a diet which leaves little or no residue, suffer from affections of the intestines which may prove fatal, whereas such effects can be avoided by adding to the food any material which leaves behind an unabsorbed residue That this is universally true of man, whose intestine is shorter in proportion and whose food is not strictly vegetable, has been very largely accepted by modern scientists

(v) *Biological value* The term biological value is applied to proteins only and its importance in dietetics has only been recently appreciated By biological value is meant that property of proteins by which they can replace the wear and tear of the body Thus when it is said that the proteins of milk have a high biological value or those of wheat have a low biological value, it is meant that milk proteins can supply the requisite material for growth at a lower figure for intake than can those of wheat Proteins of poor biological value have, therefore to be supplied in larger amounts to counteract the body catabolism than proteins of higher biological value The biological value of proteins has been expressed in figures If 100 parts of body protein can be replaced by 100 parts of a food protein then that food is said to have a value of 100 If however 100 parts of it replace only 60 parts of body protein, then it is said to have a value of 60 and so on

In ordinary dietetics we usually deal with proteins of mixed sources and the quantity consumed is usually sufficient to meet the tissue waste and, therefore, the question of 'biological value' of special proteins does not arise In the prescription of invalid dietary and under circumstances where life has to be maintained with the minimum quota of protein, the selection of the proper proteins becomes very important If a protein lacks in the amino acids (lysine, arginine, tryptophane, tyrosine), which are essential to the manufacture of human protein, that protein is absolutely useless to the body economy For example, gelatin has no tryptophane, no cysteine and very little tyrosine in its composition. Zein, a protein derived from maize, is devoid of lysine and tryptophane On the whole it has been found out that animal proteins have good supplies of the amino acids in their molecules suitable to the body mechanism while vegetable proteins have considerably less It, therefore, follows that in nutrition, animal proteins are more valuable than vegetable proteins Further, it has been noted that proteins of high biological value raise the biological values of other poorer proteins when taken with them The function of the cheese, eggs fish meat and milk proteins which we take in our diet is to render the vegetable proteins of wheat and other cereals and the pulses of greater value in nutrition than they otherwise would be

(1) Amount of food required in health

A good deal of work has been done by physiologists to determine the optimum quantities of the three proximate principles of food, the proteins carbohydrates and fats, required by human beings for the maintenance of health and efficiency No definite agreement applicable to the human race as a whole has yet been reached. The body is remarkable in adapting itself to changes in diet and it would be wrong to apply any hard and fast rules as to what the relations of proteins, fats and carbohydrates should be As proteins supply the building material to the body and as a healthy man is always doing a moderate amount of muscular work, the protein quota in food should always be considerably above the loss sustained daily, if a proper balance and growth of the body is to be maintained It has been assumed, as a result of a large number of observations that the protein in the diet of an average man should not fall below 80 grammes a day and should contain sufficient quantities of good protein (*i.e.*, of animal origin) to supply 5 per cent of the total 'calories'

ates

The carbohydrates and fats in the diet supply the energy required by the body As far as the demand of the cells for energy is concerned, it is a matter of indifference how much of the total energy required is obtained in each of these forms To the digestive organs, however, it is by no means a matter of indifference If all the energy not provided from protein were to be obtained from carbohydrate it would mean that a large bulk of food must be consumed, which would not only overload the stomach and intestines but would also be prone to undergo fermentation If, on the other hand fat be adopted as the exclusive source of energy, the limits of fat absorption would be overstepped and nausea and diarrhœa produced The absorbed fat may cease to be normally metabolised giving rise to ketosis Exclusive fat or carbohydrate food, therefore, is not good for the system though theoretically the required amount of energy can be easily supplied by any one of them individually The proportion of fat to carbohydrate may, however, vary within a wide range depending upon environment, habit, etc Thus the Eskimo takes twice as much fat as carbohydrate because his environment does not

the carbohydrates

As a rule, it is appropriate to assume that a man (or woman) who leads a quiet life at hor
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Calories necessary

According to the British Ministry of Health the diet should contain 3,400 calories with 50 gm of proteins, the British Medical Association Committee lay down 3 000 calories with 37 gm of protein

Nutrition committee report

The first part of the report of the expert Committee on Nutrition states that 2,400 calories net a day are adequate for an adult man or woman living an ordinary everyday life in a temperate climate and not engaged in manual work. This allowance is to be supplemented for various grades of muscular activity For light work it is estimated that an additional 50 calories per hour of work is needed, for moderate work, 50 to 100 calories, for hard work, 100 to 200 calories, for very hard work, 200 calories or more For pregnant women 2,400 calories are considered sufficient, and for nursing mothers 3 000 For infants energy requirements are assessed on the basis of 100 calories per kilo of body weight for the first three months of life, 90 calories from three to six months, 80 to 90 calories for six to twelve months Further it is suggested that the activities of girls from the age of 7 upwards and of boys from 7 to 11 years should be looked on as equivalent to light work, and those of boys from 11 to 18 years as equivalent to moderate work. As a general recommendation it is suggested that the protein intake of adult should not fall below 1 gm of protein per kilo of body weight, and that a part of this should be from animal sources Some animal protein is considered essential during growth, pregnancy, and lactation In the second part of the report on mineral and

Vitamins

eggs are of great service as they contain calcium phosphorous vitamins and iron. On general lines the committee is of opinion that, (i) variety in diet tends to safety so long as there is a sufficiency of protect...
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(2) Mineral Constituents

The mineral ingredients of the diet are important building material for the body This will be evidenced from the fact that the human body contains about 7 lb of mineral matter

Mineral requirements

The chief mineral substances required in the food are sodium, potassium, calcium,

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The mineral constituents cannot supply any heat to the body as they enter the body in a highly oxidised form. They are however important in regulating the production of energy in the body Thus calcium is essential in the production of muscle contraction, whether of the skeletal or the cardiac muscle Iron is essential for the normal processes of all oxidation and the production of energy by tissue cells, iodine in the production of the secretions of the thyroid gland which govern the body metabolism

No definite estimate of the quantity of mineral matters required for healthy nutrition can be given Many of the waste mineral matters of the body are excreted by the intestine, and there is no means of telling what proportion of these has merely escaped absorption, and how much has been excreted from the blood after playing a part in metabolism A rough estimate of the mineral requirements of the diet in grammes per day is given below (Hutchison and Mottram)

Phosphoric acid	3 to 4	Calcium	0.4 to 1
Sulphuric acid	2 to 3.5	Magnesium	0.3 to 0.5
Potassium oxide	2 to 3	Chlorine	6.0 to 8
Sodium oxide	4 to 6	Iron	0.015

In the ordinary mixed diet the amount of mineral matter present is about 20 grammes and therefore is usually sufficient for all the needs of the body Most of the minerals are in a state of organic combination Thus both calcium and phosphorus are present in organic combination in milk, iron in meat, sulphur in all protein-containing foods and so on Minerals seem to be utilised in the body much more easily in organic form than in inorganic form though there is evidence to show that minerals like calcium and iron are quite easily absorbed in a purely inorganic form

(3) Water

Water is an essential constituent of all protoplasm and a vitally important factor in the body nutrition The average water content of the body is about 70 per cent and this high figure is absolutely necessary to provide the body with a medium in which chemical actions can occ[illegible] ference of chemical compounds thr[illegible] portance than the ordinary fo[illegible] working of the complex biolog[illegible] constant loss of water from [illegible] is a tendency to a greater concentration of chemical compounds in the tissues, but before this can reach a dangerous concentration the sensation of thirst prompts a replacement of water This delicate reaction to concentration of the tissue is sufficient to help maintain near its optimum, the balance between water intake and output

[illegible]

Through the normal intact skin, water is not appreciably absorbed the outer layer of the mammalian skin may slowly absorb a little quantity but the passage of significant amounts inwards through the skin does not occur When ingestion becomes impossible it is difficult to supply water fast enough through other channels Rectal administration and parenteral infusion are all inadequate

The excretion of water occurs mainly by the kidneys the lungs the skin and the intestines and there are many factors which modify the rate of excretion to a considerable extent Thus if water is taken hot it favours diaphoresis, if taken in excessive quantity it may lead to diarrhœa and be rapidly eliminated If it is taken before food, almost an equal amount will be promptly excreted by the kidneys, if it is taken with or soon after food it may be retained.

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Water intake

The body receives water from various sources—ingested fluids water contained in solid foods and water produced from the complex chemical processes of metabolism. Water taken along with meals has beneficial effects upon all the digestive organs provided of course the food is well masticated It aids the digestive action of the saliva, and helps the flow of the gastric as well as the pancreatic juice It secures better absorption of food and lessens the putrefactive process of the large intestine

It would be of special interest in this connection to go into the quantity of water taken daily by the people of the tropics The various climatic influences demand a more liberal intake of water owing to a comparatively high loss of water from the body due to constant and profuse perspiration

Saderstrom and DuBois give the data regarding the intake and output of water in the daily life of an average normal individual

Water intake —

Drinking water	300 gm
Water in coffee, milk, soup etc	580 gm
Water in solid food	720 gm
Water from oxidation of 100 gm of protein	41 gm
Water from oxidation of 110 gm of fat	118 gm
Water from oxidation of 244 gm of carbohydrate	135 gm
Total	1 894 gm

Water output —

Water excretion

By kidneys	750 gm
By bowels	300 gm
By skin and respiratory passages	700 gm
Total	1 750 gm
Amount retained in the body	144 gm
Gain in the body weight	100 gm

In the tropical climates the figures of both the intake and output are considerably large Dehydration may result from low water intake or excessive water output such as may occur in hot climates Sensation of thirst normally indicates dehydration first but under certain pathological conditions it may proceed to a dangerous degree before it can be detected The superficial signs of lack of water are dryness of skin shrinkage of subcutaneous tissue and diminution in the quantity of urine In order to find out whether there is adequate supply of water to the body and proper retention measurement of the body weight is a reliable guiding factor Most physiologists will agree however that all measurements of the state of body with respect to water must be relatively empirical until the mechanism of regulation is better understood

(4) Dietetic sources of the mineral constituents

Milk and eggs are the commonest sources of calcium milk containing 1 5 gm of lime in every litre Cheese is very rich in calcium but is not largely consumed in India and probably not in other tropical countries Foods poor in calcium are meat fish, bread fruits and potatoes

Calcium

An infant requires about 0 3 gm (5 grains) of lime daily The adult, owing to cessation of growth of the bones, requires relatively
calcium reed of the mother is high for
pregnancy the fœtus requires about 0.3 gm
eggs as foods for growing children and
from these facts

Magnesium

Magnesium is usually present in foods in the same proportion as calcium Milk also contains magnesium and meat more magnesium than calcium

Iron

Iron is usually present in food in an organic form It is mainly excreted in the fæces and hence a definite estimate of the daily amount required by the body is not possible A normal diet contains about 20 mgm or more of iron and this quantity is sufficient to meet all physiological demands.

The amount of iron in different foods varies widely For example the following quantities of iron in milligrammes per 10 grammes are contained in certain common foods

Green vegetables	20 to 40
Peas dried	57
Milk	0.2
Beef and eggs	30
Rice, polished	09

From the results available, it may be concluded that red meats like mutton and beef and yolk of eggs are very rich in iron as also vegetable foods like rice, potatoes spinach wheat. As regards an ordinary mixed diet, it may be said that the amount of iron which it contains is roughly proportional to its richness in protein, for these two constituents tend to run parallel to each other

An abundant supply of this metal is of special importance to growing children and to women during pregnancy The new born infant starts life with a fairly rich store of iron from the mother, and as long as its sole food is milk, it lives on an iron poor diet

Sodium is obtainable from the animal group of foods whereas potassium is contained chiefly in the vegetable group Sodium is absorbed in the form of sodium chloride and, as is well known this is consumed to a much greater extent than is ever required by the body The minimum requirement of these salts is from 1—2 gm per diem but an ordinary mixed diet contains 3 or 4 times this amount and hence deficiency in these salts is not likely to occur

Phosphors enters into the composition of all cell nuclei and it is abundantly present in the bones and in the central nervous system Wherever growth is going on rapidly a large supply of phosphorus will be required in the food otherwise development will be seriously impaired The phosphorus contained in foods is for the most part present in an organic form part in inorganic form as phosphates of the alkalies or alkaline earths There is reason to believe that the organic forms are more valuable for contributing to the growth and repair of the tissues, nucleoproteins (liver kidney, sweetbread) phospho-proteins (milk, cheese yolk of egg) lecithin (yolk of egg) and other phosphatids and phytin (hexaphosphoric ester of inosite and is found in bran leguminous seeds and tubers) are all rich sources of organic phosphorus Fresh vegetables are also good sources of phosphorus

Sulphur is present in organic combination chiefly in proteins

Chlorine is ingested almost entirely in the form of sodium chloride

Iodine is present in small quantities in fresh water plants water and land plants The amount required in the diet daily is estimated to be about 45 microgrammes for an adult and 150 microgrammes for a child

Fluorine and *silica* are present in the body in small quantities chiefly in the teeth and bones Vegetable foods and especially the cereals are the most abundant available sources.

A satisfactory diet therefore must contain suitable quantities of —

(a) Proteins which should be digestible and absorbable and which should have a positive biological value
(b) Carbohydrates
(c) Fats
(d) Mineral constituents including salts iodine etc
(e) Vitamins
(f) Water
(g) A sufficient roughage.

The diet must also be free from poisonous substances Certain individuals are particularly sensitive to certain articles of diet and these should be particularly avoided to avert the unpleasant and sometimes dangerous anaphylactic symptoms

Taking a broad view one can safely regard a diet as being suitable when large groups of human beings who have lived on it for generations are healthy and long lived The ... different
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of Asiatic races who are mainly vegetarians however does not bear out the contention of these physiologists as some of these races are just as healthy and long lived as the

people of the West who take much larger quantities of animal food. It must not be forgotten that the so-called vegetarians are not t-
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connection. an ordinary adult who has great powers of adaptability there can be no doubt that in the case of children adolescents and pregnant women, it is far safer to adopt a high protein standard than a low one No risk must be run of providing too l ttle build ng material for the growing organism

2. The Indian Dietary

Common Indian dietary

It will be interesting in this connection to consider the dietary of Indians and to see how far this diet comes up to the satisfactory standard The importance that an Indian attaches to his diet is hardly realised by Western practitioners It is not uncommon to find a practitioner writing up prescriptions for medicines without any directions as to the nature of the diet his patient should take The patients often remain dissatisfied in this respect and may lose faith in the physician

The Indian diet has largely been founded on economic principles but also partly on the long experience of climate on social customs etc, and is now a sound working principle based on a fight against the poor nature of the soil and the paucity of rains Two meals are eaten during the day the morn ing meal generally consisting of rice and *dal* (pulses) or unleavened bread and curdled milk, the next meal consists of rice with *dal* or vegetables or unleaven bread with vegetables or meat curry In villages the ryot often drinks diluted milk or curds In towns during the hot weather some savoury food is taken during the afternoon Indians are very partial to fruit and in Northern India fruit is eaten before or between these meals Meat is rarely taken more than twice a week but amongst Brahmins Buddhists and Jains meat is not eaten in any form. The nitrogenous portion of the diet is largely made up by milk and *dals* or pulses We will now discuss these diets in some detail and try to show how far these items of diet supply the necessary proximate principles

Carbohydrate

The staple food of the people of India is rice According to the report of the Famine Commission out of 191 millions people in the country nearly 68 millions are rice eaters In the Pun ab U P and O dh
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Bombay and the northern parts of Madras, the two varieties of large millets (*jowar* and *bajara*) form the principal food In Mysore the ordinary food is the small variety *ragi* but rice and wheat are also taken Baluchisthan the North Western Frontier Province and in the higher Himalayas a good deal of maize flour is also eaten along with a certain amount of rice

The carbohydrate food of the Indians therefore can be divided into two types —

(A) Rice—in the rice-growing areas of Bengal Madras Southern India and in sub-montane areas of Nepal Kashmir and British India

(B) Flour—as unleavened cakes (*chapatties*) The bread is made from wheat in the Punjab, millets over Central and Southern Ind a and from maize in the N W F Province and B har

Sugary foods Sugar is obtained in India from
from various palms, *e g* the date. Coarse sugar
poor classes whereas all sorts of refined sugars
sections of the population The Indians are p
they can afford it will consume a considerable amount of sugar during the day

The variety of sweets eaten are enormous and consist of mixtures *of sugar with* different preparations of milk curds rice *suji* flour, cocoanut Milk is often sweetened with sugar before taking

(*a*) *Milk and Milk derivatives* Milk is the most popular protein consumed in India. As a matter of fact cow's milk is the staple food of *the ryot in most of the rural districts* of India In towns most of the milk sold is a mixture of cow's and buffalo's milk well diluted with water Cow's milk is considered to be strength building fattening and beneficial in gastric conditions Buffalo's milk, goat's milk etc, are also used in different parts of India

Milk Preserves

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Dahi or curdled milk is one of the most important milk derivatives *It is* nothing but ordinary milk which has been allowed to undergo lactic acid fermentation and coagulates into a creamy white gelatinous mass like junket and has a pleasant acid taste. Curdled milk is better borne by the stomach as it has been already coagulated and its thick consistency makes it possible to be broken up by mastication Its acid taste makes it more refreshing than milk and when diluted it makes a delicious cool drink in the hot weather Metchnikoff's view of introducing into the alimentary canal bacteria that will inhibit the proteolytic action of the organism of putrefaction by virtue of the lactic acid produced by them seems to have some support by this universal custom of taking curdled milk Potcheese (*chhana*) is made by coagulating milk by citric acid, *i e* the juice of the lemons and removing the whey It must be used fresh as it deteriorates very quickly Whey (*ghol*) is a greenish yellow coloured liquid with a sweet acid taste. Whey contains

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(*c*) *Fishes* There are numerous species found in the Indian rivers these vary in quality some are of fine flavour (*Hilsa, Mrigal Katla* and other fat fish) while others are poorer in quality (*Koi Singhee* and other lean fish) Fish is an important article of food in Bengal where very little meat is taken. Sea fish is taken by certain sections of the population living along the coasts

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3. Adaptation of Diet in the Tropics

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The proportion of protein fat and carbohydrate varies considerably in the diets of different races, depending largely on the type of food available and also upon the customs existing in particular localities The prevailing diet of the masses in the tropics is derived largely from vegetable sources and carbohydrates generally predominate in it Nearly a century ago, Chevers thought that the Hindu dietary with a very moderate quantity of animal food was the one most suited for a tropical climate

Biological value of Proteins

The protein requirement of the tropical races has been the subject of intensive investigation and research by a large number of works in India and other tropical countries but no definite conclusions have been drawn It has been pointed out that in many parts of the world those who consume a diet with high protein content have a better physique and are more virile than others of the same race who for one reason or another, consume

The variety of sweets eaten are enormous and consist of mixtures of sugar with different preparations of milk curds rice *suji* flour cocoanut Milk is often sweetened with sugar before taking

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The adaptation which man is called upon to make in the tropics is primarily one of heat regulation The problem of diet is intimately connected with the problems of heat regulation body temperature and metabolic rate The question of the suitability or other wise to the tropical climate of the common foodstuffs available in the tropics is not satis factorily answered. Nature offers fat and protein in the arctic regions and carbohydrates at the equator, and man in these areas has always accepted them as his staple foods. It is not clear as to what is the optimum or ideal to be a med at with a view to effecting a suitable adjustment to the climate

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(1) Alcohol

Indulgence in alcohol is another factor which may advantageously be considered under this section Though alcohol is *not an article of food, it is commonly taken* as a drink along with food and this is perhaps one of the most important dietetic errors in the tropics Europeans suffer most from the alcohol habit though in recent times a good section of the Indian commun ty has also contracted the habit The plea usually put forward is that alcohol is necessary for the maintenance of health and that without its stimulating influence no strenuous work can be carried on satisfactorily Others consider it a stimulant which is necessary in the tropics after a day's hard work It is also believed to be a protective from malaria and bowel and other diseases These ideas have al been shown to be erroneous Though one cannot deny to alcohol the right to be regarded as a food in the scientific sense of the term it cannot be regarded as a food of great *importance for although it is able to replace fat and carbohydrate it cannot be converted* into these while its secondary effects on the nervous and vascular systems counteract, to a large extent the benefits derived from the production of heat and energy by its oxidation Many writers have produced evidence to show that it is not favourable to the production of healthy mental labour Alcohol has no influence on physical labour and sustained muscular effort as is generally supposed It may even do harm by paralysing the sense of fatigue which is the natural check on excessive exertion

On the other hand whenever the proportion of alcohol circulating in the blood becomes greater than the cells can rapidly deal with it acts as a protoplasmic poison The brain cells seem to be peculiarly sensitive to the paralysing action of alcohol so that the brain is the first to show the effects of an overdose and intoxication results If this overdosage is kept up for a very long time the highly organised and delicate brain cells would naturally become the seat of various degenerative changes A certain degree of dulling or even paralysis
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The excretion of undecomposed alcohol through the kidneys may also act as an irritant and bring about changes in structure and ultimately may produce chronic *nephritis* It has injurious effects on the gastro intestinal tract and part cularly on the liver Alcohol also paralyses the blood vessels and thus interferes with dissipation of heat from the body It renders people liable to heat stroke and alcoholism is one of the prolific causes of this cond tion in the tropics

It will thus be seen that alcohol is an unnecessary article of diet in normal health and is not truly *beneficial to the system but is actually injurious from the physiological* point of view *Alcohol there is little doubt is a potent factor in shortening the life* and undermining the health of the majority of Europeans in the tropics Alcohol strongly predisposes to liver abscess heat stroke and tropical neurasthenia It makes the habitue a bad subject for surg cal operations and lowers the resistance of the tissues to intercurrent infections Obesity diabetes and other disorders of metabolism l ke gout etc have all been ascribed to the excessive ingest on of alcohol

The injurious effects of over indulgence in alcohol in hot countries cannot be over estimated It has been approximately ascertained that from 1 to 1½ ounces of absolute alcohol is about the amount that can be utilized as a food or completely oxidized in the body in twenty four hours though some put the amount at 3 ounces and consider that in that quantity it is a food

If we accept the first that amount of alcohol would be represented by the following quantities of the more frequently used alcoholic drinks Brandy or whisky (40 to 47 per cent alcohol) 3 fluid ounces port sherry or other strong wines (about 20 per cent

alcohol), 7 ounces claret hock champagne, and other wines (5 to 10 per cent alcohol) 15 ounces or a tumblerful and a half, strong ale (bottled) (10 per cent alcohol), 20 ounces, or one imperial pint.

Alcohol is a chemical irritant and the amount of irritation on the nerve endings, mucous membrane and other organs is entirely proportionate to the degree of dilution and the quantity taken above the amount specified. Alcohol is rapidly oxidized in the body as result of physical exertion and under such conditions more can be consumed without injurious effects than in case of an individual with sedentary habit. While total abstinence may not be essential in warm climates alcohol in moderation may be taken stimulating and restorative effects. It should not be taken during the hotest part of the day or when it is intended to be out in the heat of the sun

Alcohol an irritant

(2) Dietetic Errors of Indigenous Races

The chief defects consist in the excessive bulkiness and low nutritive value of the diets. People who live chiefly on rice often take 30 to 40 oz daily, this when cooked forms a very bulky diet which causes distention of the stomach and is incompletely digested. McCay who carried out important investigations into Indian diets made the following observations —(1) The absorption of proteins from cooked rice is actually diminished when excessive quantities are eaten for example 8½ gm were absorbed when 19 oz of rice were eaten daily, but only 6½ gm when 30 oz were consumed. The larger ration does not make up for the poorness of proteins of the diet but rather the reverse while the excess of carbohydrates upsets the balance of the diet (2) Certain vegetable sources of protein are unsatisfactory from a diet of millets dal and vegetables containing 16 gm of protein in all only 9½ gm were absorbed whereas from a diet of wheat containing 16 gm of protein as much as 13 gm were absorbed (3) Unsuitable methods of cooking and disorders of the alimentary system caused a reduction in the absorptions of proteins (4) Great variations in physique and fitness were found among the races using different diets. Europeans and Sikhs who absorbed over 0.25 gm of protein per kg of body weight were far more robust than Bengalis who absorbed only 0.11 gm per kg. The average Sikh diet approaches closely to good European standards it consists of milk 3/4 pint wheat 24 oz butter or ghee 2 oz dal 3 oz vegetables 6 oz and meat 4 oz. An unexpected finding was that the low protein absorption of the Bengalis was associated with increased prevalence of degenerative diseases of the kidneys. The reason for this is probably malnutrition of the kidney cells

The nutritional defects of indigenous populations are easy to discover but difficult to rectify, they are closely associated with poor economic standards of life which in turn are connected with social customs, especially early marriage and unrestricted procreation of children. So long as immature boys and girls marry and proceed to have large families before they are able to maintain them there is no prospect of economic improvement any increase in the production of food will quickly be neutralised by a corresponding increase in the population. The solution of the problem lies in a rational education directed towards showing the rising generation how to adapt themselves to their environment by later and more provident marriages or by limiting the number of children in some other way. The chief dietetic error which prevails among the richer members of the tropical communities consists in excessive consumption of carbohydrates, especially in the form of easily absorbable sugars. This fault when combined with lack of exercise leads to obesity and finally to diabetes

5. Diet in the Tropics

(1) Diet in Disease

Diet plays a very important part in the treatment of disease in the tropics. Diet may be considered in the light of a therapeutic agent and like all other remedial agents has a limited place in therapeutics and should not be considered as a panacea for all ailments. Dietetic treatment is specially important in a particular group of disorders and we will confine our attention to these disorders primarily. The principles of feeding will only be outlined the detailed regime will naturally have to be laid down by the physicians with special reference to the particular type of requirement

The prejudices of patients and the superstitious beliefs existing in India sometime make it very difficult for the physicians to prescribe a regular routine

Further a predominantly protein diet is likely to leave a very imperfect residue as such diet is always better absorbed In the tropics the general musculature of he body as well as the intestinal muscles are not kept in that tone which is common in the residents of the cold countries and hence constipation results Habitual constipation leads to intestinal stasis and the absorption of toxic end products of protein cleavage Gradually the constitution gets undermined, bowel troubles supervene and mental disturbances in the from of neurasthenia, failure of memory irritability etc result It is also probable that sprue and appendicitis so commonly seen amongst the Europeans and so makedly absent in the indigenous races of the tropics been some relation to auto intoxication from the bowels

(1) Alcohol

Indulgence in alcohol is another factor which may advantageously be considered under this section Though alcohol is not an article of food it is commonly taken as a drink *along with food and this is perhaps one of the most important dietetic errors in the* tropics Europeans suffer most from the alcohol habit though in recent times a good section of the Indian community has also contracted the habit The plea usually put forward is that alcohol is necessary for the maintenance of health and that without its stimulating influence no strenuous work can be carried on satisfactorily Others consider it a stimulant which is necessary in the tropics after a day's hard work It is also believed to be a protective from malaria, and bowel and other diseases These ideas have all been shown to be erroneous Though one cannot deny to alcohol the right to be regarded as a food in the scientific sense of the term it cannot be regarded as a food of great importance for although it is able to replace fat and carbohydrate it cannot be converted into these while its secondary effects on the nervous and vascular systems counteract, to a large extent the benefits derived from the production of heat and energy by its oxidation Many writers have produced evidence to show that it is not favourable to the production of healthy mental labour Alcohol has no influence on physical labour and sustained muscular effort as is generally supposed It may even do harm by paralysing the sense of fatigue which is the natural check on excessive exertion

On the other hand whenever the proportion of alcohol circulating in the blood becomes greater than the cells can rapidly deal with it acts as a protoplasmic poison The brain *cells seem to be peculiarly sensitive to the paralysing action of alcohol* so that the brain is the first to show the effects of an overdose and intoxication results If this overdosage [illegible] naturally

leads to a diminution of the chemical energy of the cells which interferes with the ord[illegible] course of metabolism and may result in chronic disease The metabolism of fat is most likely to be interrupted and hence alcoholism is a common cause of fatty degeneration

The excretion of undecomposed alcohol through the kidneys may also act as an irritant and bring about changes in structure and ultimately may produce chronic nephritis. It has injurious effects on the gastro intestinal tract and particularly on the liver Alcohol *also paralyses the blood vessels and thus interferes with dissipation of heat* from the body It renders people liable to heat stroke and alcoholism is one of the prolific causes of this condition in the tropics

It will thus be seen that alcohol is an unnecessary article of diet in normal health and is not truly beneficial to the system but is actually injurious from the physiological point of view *Alcohol there is little doubt is a potent factor in shortening the life* and undermining the health of the majority of Europeans in the tropics *Alcohol strongly* predisposes to liver abscess heat stroke and tropical neurasthenia It makes the habitue a bad subject for surgical operations and lowers the resistance of the tissues to intercurrent infections Obesity diabetes and other disorders of metabolism like gout etc have all been ascribed to the excessive ingestion of alcohol

The injurious effects of over indulgence in alcohol in hot countries cannot be over estimated It has been approximately ascertained that from 1 to 1½ ounces of absolute alcohol is about the amount that can be utilized as a food or completely oxidized in the body in twenty four hours though some put the amount at 3 ounces and consider that in that quantity it is a food

If we accept the first that amount of alcohol would be represented by the following quantities of the more frequently used alcoholic drinks Brandy or whisky (40 to 47 per cent alcohol) 3 fluid ounces, port sherry or other strong wines (about 20 per cent

alcohol), 7 ounces claret hock champagne and other wines (5 to 10 per cent alcohol) 15 ounces or a tumblerful and a half, strong ale (bottled) (10 per cent alcohol) 20 ounces, or one imperial pint

Alcohol is a chemical irritant and the amount of irritation on the nerve endings, mucous membrane and other organs is entirely proportionate to the degree of dilution and the quantity taken above the amount specified. Alcohol is rapidly oxidized in the body as result of physical exertion and under such conditions more can be consumed without injurious effects than in case of an individual with sedentary habit While total abstinence may not be essential in warm climates alcohol in moderation may be taken stimulating and restorative effects It should not be taken during the hottest part of the day or when it is intended to be out in the heat of the sun

(2) Dietetic Errors of Indigenous Races

The chief defects consist in the excessive bulkiness and low nutritive value of the diets People who live chiefly on rice often take 30 to 40 oz daily this when cooked forms a very bulky diet which causes distention of the stomach and is incompletely digested McCay who carried out important investigations into Indian diets made the following observations —(1) The absorption of proteins from cooked rice is actually diminished when excessive quantities are eaten for example 8½ gm were absorbed when 9 oz of rice were eaten daily but only 6½ gm when 30 oz were consumed. The larger ation does not make up for the poorness of proteins of the diet but rather the reverse hile the excess of carbohydrates upsets the balance of the diet (2) Certain vegetable urces of protein are unsatisfactory from a diet of millets dal and vegetables containing gm of protein in all only 9½ gm were absorbed whereas from a diet of wheat contain r 16 gm of protein as much as 13 gm were absorbed (3) Unsuitable methods of cooking and disorders of the alimentary system caused a reduction in the absorptions of proteins (4) Great variations in physique and fitness were found among the races using different diets. Europeans and Sikhs who absorbed over 0.25 gm of protein per kg of body weight were far more robust than Bengalis who absorbed only 0.11 gm per kg The average Sikh diet approaches closely to good European standards it consists of milk 3/4 pint wheat 24 oz butter or ghee 2 oz dal 3 oz vegetables 6 oz and meat 4 oz An unexpected finding was that the low protein absorption of the Bengalis was associated with increased prevalence of degenerative diseases of the kidneys The reason for this is probably malnutrition of the kidney cells

The nutritional defects of indigenous populations are easy to discover but difficult to rectify, they are closely associated with poor economic standards of life which in turn are connected with social customs especially early marriage and unrestricted procreation of children So long as immature boys and girls marry and proceed to have large families before they are able to maintain them there is no prospect of economic improvement any increase in the production of food will quickly be neutralised by a corresponding increase in the population The solution of the problem lies in a rational education directed towards showing the rising generation how to adapt themselves to their environ ment by later and more provident marriages or by limiting the number of children in some other way. The chief dietetic error which prevails among the richer members of he tropical communities consists in excessive consumption of carbohydrates especially n the form of easily absorbable sugars This fault when combined with lack of exercise ads to obesity and finally to diabetes

Diet in the Tropics

(1) Diet in Disease

Diet plays a very important part in the treatment of disease in the tropics t may be considered in the light of a therapeutic agent and like all other edial agents has a limited place in therapeutics and should not be considered panacea for all ailments Dietetic treatment is specially important in a icular group of disorders and we will confine our attention to these disorders arily The principles of feeding will only be outlined the detailed regime aturally have to be laid down by the physicians with special reference to articular type of requirement

he prejudices of patients and the superstitious beliefs existing in Ind ne make it very difficult for the physicians to prescribe a

deficiency in many essential food substances and with a pregnancy superadded may be greatly reduced by judicious dieting This problem does not affect the mother alone, the growing fœtus also suffers serious results

The early fœtal growth takes place at the expense of the maternal tissue and there is always an extravagant breaking down of it to enable the fœtus to get its requirements. At a later stage the fœtus derives its nutrition from maternal food Over and above this many chemical substances which are essential for its growth are present only in small quantities in maternal organs and they cannot be synthesised by either the mother or the fœtus A liberal supply of these substances (or their effective precursors) must be from the food the mother takes Ordinary diets vary widely so far as the energy bearing factors the proteins the fats and the carbohydrates are concerned and yet they may remain compatible with good maternal and fœtal health The trouble arises, when there is unbalanced dietary and a deficiency of factors essential to proper structure function and even to life of the mother and of the offspring Among these are calcium phosphorus iodine iron and vitamins A and D A pregnant and lactating woman has to supply calcium to the fœtus from her own store Calcium and phosphorus of different foods are retained by the body to different extent and the retention is greatly influenced by the presence of vitamin D Cereals such as oatmeals and cereal embryo which are rich in calcium and phosphorus are anticalcifying and along with them a well balanced amount of calcium retaining factor in form of milk and cod liver oil (which ensures a good supply of vitamin D) should be ingested Cod liver oil also supplies vitamin A which increases the resistance to infection

The significance of supplying iron to the pregnant mother is that the fœtus takes away iron from the mother in order to enable it to store iron in the liver to tide over the milk diet period when it gets a deficient amount of iron Consequently a failure to supply mother at such a time with sufficient iron will tell upon herself and the child as well The daily diet should consist of food rich in iron such as meat egg yolk calf's liver green vegetables etc

Iodine is of importance both to the mother and the offspring A deficiency of iodine in pregnancy results in cretinism in the offspring and simple goitre or myxœdema may follow numerous pregnancies in a mother Sea fish or any kind of living matter from the sea and cod liver oil should be included in the diet

According to Mellanby the diet of pregnancy and lactation ought to include the following

2 pints of milk daily

1 or 2 substantial servings of green vegetables—cabbage spinach or lettuce daily

1 or 2 eggs or egg yolks daily

An apple or orange or some fresh fruit daily

Sea fish twice or more a week

Cod liver oil may be taken 2 teaspoonfuls daily

The rest of the diet can be made up as the expectant mother desires

Green Armytage recommends for the Indians the following diet with the addition of radiostoleum and Parrish s food

Cereals	—	*Dhenki* (home pounded) rice *atta* (whole meal flour) and *suji*
Vegetables	—	*Sak* (green leafy vegetables) in all forms except fried *Sobji* (green vegetables etc) bean, pumkins cucumber brinjal green peas squash cabbage cauliflower tomato etc
Fruits	—	All fresh or stewed
Eggs	—	Ducks or hens in any form except fried
Fish	—	Mud fish like—*kai magur singee*
Meat	—	Mutton chicken liver, kidney etc
Fats	—	Oils butter ghee—sparingly
Milk	—	Fresh goat s or cow s in any form—plain *dal* or *ghol* Avoid buffalo s milk
Sweets	—	Honey molasses jam jelly marmalade No pastry no cakes
Fluids	—	Water ad lib cocoanut water weak tea, coffee aerated water home made lemonade or lime juice

It is important to avoid any excess in the individual articles of diet as well as in the total intake of food. The idea that a pregnant woman needs large quantities of food is erroneous. Excess of fat in the diet should be avoided not only during the early months when vomiting is a troublesome symptom but also during the subsequent months of pregnancy. Vomiting is due at least in part to excessive fat intake which must be limited.

Diet and toxaemias of pregnancy

The position regarding the relationship between diet and toxæmias of pregnancy has been summarised by Mellanby. "It is unfortunate that there is no established clinical or experimental evidence that malnutrition is responsible for those toxæmias of pregnancy which include albuminuria, pre-eclamptic toxæmia and eclampsia itself. In spite of the absence of such evidence I wish to plead that future investigators of these problems will give some attention to this aspect of the case. The hypothesis that such toxæmias are due to the production of toxic substances by the fœtus and placenta has not been fruitful. On the other hand, there is very indication that they are due to abnormal metabolism and since so many defects in metabolism are now known to be nutritional in origin the chances that such a factor is the basis of eclamptic conditions are large.

"The final teaching based on the foregoing facts is that proper nutrition is essential to healthy childbearing and that the diet should include throughout pregnancy and lactation a sufficiency of what are known as protective foodstuffs. When plenty of these are taken there is every reason to believe that the rest of the diet will take care of itself."

In abnormal cases, the diet can be dealt with under the following headings —

1 Constipation—It is often benefited by increasing fluid intake and the amount of fruit and vegetables in the diet. It is better to avoid taking purgatives of drastic griping type. Saline aperients or lubricants might be used with good results if at all needed.

2. Albuminuria—In pre eclamptic cases the dieting should be drastic, the solid part of the diet being epsom salts and glucose and the liquid part water. In milder cases, if they respond to a few days treatment in bed on a rigid diet, the pregnancy may be allowed to continue but the diet should be absolutely protein free. Fruits and vegetables can be taken freely and milk, cooked in any form, is well tolerated.

3 Pyelitis appears about the 20th week and frequently simulate appendicitis. Massive doses of alkalies with a ketogenic diet often help the patient to tide over an attack.

Diet during lactation

During lactation the regulation of mother's life is of the utmost importance. The diet should be of plain nutritious food. An ordinary well balanced diet is best for producing a good supply of milk during lactation period. There are no galactagogues known to be of positive value. In cases where milk is poor or deficient in quantity, thick malt extracts a tablespoonful three times a day may be prescribed. Where the fat is deficient plenty of butter, cream and olive oil may be added to diet.

Diets containing milk proteins and animal proteins are better for producing milk than those containing vegetable proteins. Over feeding never increases the quantity of milk. Cow's milk protein is the best form to increase the milk production and to protect the mother's tissue. Besides the food factor plenty of rest and daily bath, a daily walk in open air and as much outdoor life as possible are essential. Tea or coffee should be taken in moderation and anything containing vinegar, spices, mustard or rich and complicated dishes should be avoided.

(3) Diet in Infancy and Childhood

It is seldom if ever necessary to have recourse to any artificial means of nourishing the newly born infant. It is the baby's birth right to be nursed by its own mother and breast feeding is always the best for both the mother and the child. It gives the greatest security against intestinal disturbances and infection which are the commonest troubles with the new-born. The child is more strong and vigorous as compared to those artificially fed and better adapted to surroundings. The infant should be nursed in this way for at least two months if not longer.

Diet in infancy

When for some condition or other either with the mother or the child breast feeding is contraindicated the baby may be fed artificially. There is however no perfect substitute for breast milk. Although the results of careful artificial feeding are satisfactory the problem is beset with difficulty. When a child is called upon to digest food of a different form and build up the body from materials of different quality he naturally starts at a disadvantage. The younger the child, the greater is the difficulty. Before substituting any form of artificial food for mother's milk the following points should be considered very carefully.

1 The choice of food
2 The method of preparations
3 The amount of food required in twenty four hours
4 The size of each feed
5 The interval between each feed

Cow s milk, goat s milk and ass s milk may be used for the purpose and of these, the cow's is the most generally used From a comparison between the composition of cow s milk and that of breast milk it appears that cow s milk contains a large excess of protein and salts but too little sugar, the fat is in about the same proportion. In order to make it of the same proportion as the human milk, it should be diluted with water and some fat and sugar be added to it One heaped tablespoonful of sugar of milk and half an ounce of cream added to half a pint of cow s milk, and made up to a pint with water is however, a good substitute.

Not all infants even if normal and healthy can be fed in the same way The food should be modified as regards the quantity of each ingredient—fat sugar and protein in such a way as to suit the requirements of the individual child

As regards the amount at each feed it is customary to begin with 3 ounces this may be raised to 4 ounces at the end of first month 4½ during second month and so on Approximately a child will take 1 to 2 ounces more at a feed for every month of age till 8 or 9 ounces

Intervals between each feed may be four hours but what is the most essential is the regularity The child should never be waked up at night for its feeds

Various patent milk preparations are on the market but these should be avoided whenever possible Excellent results may be obtained by using a milk composed of one part of condensed milk to two or three parts of evaporated milk when diluted with seven or more parts of water Dried milks are now extensively used in warm climates and when packed in hermetically sealed tins they keep well They should be kept dry free from insects and in their original containers

It is sometimes very useful to add some additional factors to the artificial diet Cod liver oil should be started at three or four months in amount of 5 to 20 drops twice daily and continued till the age of eighteen months Fruit juice should also be added at least two teaspoonfuls daily and gradually increased

Indications for special modifications are —1 Flatulence and habitual colic are invariably due to over feeding—the food being given very rapidly most often at too frequent intervals 2 Curds in stool—This is generally caused by feeding the baby on an unsuitable mixture or when the digestive power of the child is weak. The difficulty may be remedied by boiling the milk and dilution 3 Vomiting loss of appetite constipation and diarrhœa are other difficulties in artificial feeding and they can always be dealt with by attaining the proportion of all the ingredients

A knowledge of nutrition of a growing child as regards both the amount and kind of food necessary for proper growth and maintenance of health is very essential. The points to be noted in this connection are—
Its constitution *i e*, (*a*) vitamin (*b*) salts (*c*) proteins, (*d*) fats (*e*) carbohydrates and (*f*) water

The forms in which these elements are to be provided.

The relative proportions of the various elements and the total daily amount of each.

Under modern conditions we are faced with the difficulty of *formulating* a well balanced dietary for children

The ideal diet consists of fresh milk, cream butter cheese, curds eggs, etc.

Cereals	—	Wholemeal flour wheat or rye—given in form of bread or cakes.
Vegetables	—	Green vegetables and tubers
Fruits	—	Oranges apples plums bananas etc
Sugar	—	Pure honey
Meat foods	—	Lamb chicken rabbit calves liver may be given occasionally

In the ordinary way the diet is laid down empirically and attention is given to the quality of the food, the quantity being determined in a healthy child by the appetite The real test of the value of a diet is its clinical results

The estimated requirement which determines the necessity of a generous supply of food throughout childhood and one relatively in excess of that required for the adult may be quoted shortly as follows —45 calories per pound body weight at one year, gradually decreasing to 36 calories per pound at six years and remaining at this figure until puberty

(4) Invalid Diet in Tropics

A good supply of fresh milk must be provided in every hospital Another important practical point is that invalid diets are often deficient in the anti scorbutic vitamins, a standing order should be observed in all hospitals that every patient who is on an invalid diet must be given the juice of an orange daily or a corresponding dose of vitamin C in some other form The prejudices of patients may give rise to a certain amount of difficulty Many of them regard rice as the only suitable staple article of diet so that a good deal of persuasion may be needed to induce them to take other food. Many Indians regard [illegible] that the [illegible] use they [illegible] usually [illegible] suitable [illegible] food, does not cause diarrhoea in the tropics more than in cold countries Milk in the tropics is often boiled for a longtime, care must be taken to ensure that it is just brought to boiling point and then cooled (*Tropical Medicine*—Rogers & Megaw, 1935)

6. Glucose (Dextrose)

Historical and General

Dextrose or glucose is one of the most important food stuffs and in disease it is of great value The origin of the present day dextrose therapy in medicine dates to Hippocrates. His aphorisms advise liberal quantities of honey or fruit syrups for the undernourished and the convalescent This knowledge was handed down to the Romans and honey was introduced in infant feeding in the second century A D to relieve the symptomatology of "inanition fever" Grape sugar and glucose are the oldest and perhaps the most apt synonyms of dextrose.

Chemistry

Dextrose, was first obtained in pure form by a German Chemist in the middle of the seventeenth century It was prepared on a commercial scale in the early part of 19th century by hydrolysing starch with dilute acids and this still forms the basis of its commercial production from Indian corn (maize) One hundred parts of water dissolve 82 parts of dextrose at 20-25°C. Dextrose is approximately three fourths as sweet as cane sugar

Solid dextrose is normally a mixture of two isomers The two isomers differ only in physical properties and may be separated by careful crystallization but this is of little practical importance, since the chemical and physiological behaviour of both forms is alike

(1) Physiological Considerations

Dextrose is the first carbohydrate to be formed in plants and is the primary sugar from which higher carbohydrates are derived. It is the form into which all carbohydrates must be converted before utilisation by the animal body There is something in the atomic arrangement of dextrose molecule which makes it fundamentally important to both plant and animal kingdoms.

Presence in animal body

The presence of dextrose in the blood stream was first detected in diabetics in 1775. In 1855 it was described to be present in the normal blood Dextrose is supplied to the body mainly in the form of sugar and starch foods which are broken down into monosaccharides before absorption into the blood stream Maltose is reduced to dextrose by digestive enzymes, sucrose is broken down into one, molecule of fructose, lactose or milk sugar is similarly broken into dextrose and galactose Dextrose thus constitutes by far the largest proportion of the monosaccharides absorbed into the blood stream

Absorption.

Dextrose itself on ingestion is rapidly absorbed from the small [illegible] any previous digestion Each one of the m[illegible] About 0.8-0.85 gm of dextrose are abs[illegible] absorption is independent of the co[illegible] dextrose in the intestines. The rate of dex[illegible] however, are variable factors probably Th[illegible] into blood stream is complex

After absorption, the monosaccharides are transported by the portal vein to the liver where they are converted into dextrose through the intermediary stage of glycogen. In the liver most of the dextrose is synthesized into glycogen but some passes into the systemic circulation for distribution to and utilisation by the tissues After ingestion of *90 to 100 gm of dextrose by normal fasting persons*, approximately 70 to 80 per cent of the dextrose is stored as glycogen and only 20 to 30 per cent is burned by the tissues for energy purposes If very large quantities are administered the dextrose in excess of that assimilable by the liver and tissues for glycogen synthesis or oxidation, is converted to and stored as fat

The capacity of an individual to utilize or tolerate dextrose is the dose which may be administered without producing glycosuria The rate of utilization of dextrose by the normal human body was found to be 0 8 to 0 9 gm per kilo body weight per hour Continuous intravenous infusion of dextrose solution at the rate of utilization of dextrose does not produce glycosuria in normal persons. Ingestion of as much as 500 gm of dextrose at a time does not result in glycosuria. The high rate of absorption and utilization of dextrose as well as the high renal threshold render it the best tolerated sugar Accurate determination of the ability of the body to utilize dextrose in health and disease, are now possible and dextrose tolerance tests, have been standardized. These tests are invaluable to the physician in estimating disturbances of carbohydrate metabolism. The current destrose tolerance test consists in evaluating the blood sugar and testing the urine for dextrose before and at half hourly intervals after the ingestion of 100 gm of dextrose. [illegible] level it indicates a low dextros [illegible] Various factors such as preced [illegible] f the subjects for *the test are g* [illegible] vious to dextrose tolerance test, [illegible] ministration of a high carbohyd [illegible] tolerance of the person for de [illegible] nifest itself in a hyperglycæmic dextrose tolerance curve in a normal person

The most favourable conditions for a dextrose tolerance test include a previously unrestricted diet, and the elimination of physical and emotional disturbances before or during the test

More recently modifications in the dextrose tolerance test have been suggested in order to eliminate the variations in the process of absorption and some authorities advocate intravenous injection of dextrose The one hour two dose dextrose tolerance test has been introduced Most consistent and precise results are said to be obtained by administration of 50 gm of dextrose at half hourly interval instead of single large dose and testing the blood and urine for sugar one half hour after each dose.

There are certain conditions which modify the rates of glycolysis and dextrose utilisation by the tissues and the hormones are the most important factors from this point of view The animal organism is unable to utilise dextrose without insulin The cells of the islands of Langerhans of the pancreas are sensitive to the concentration of blood *sugar* Their activity is stimulated by the presence even of a very slight excess of dextrose in the blood As a result more insulin is produced in order to mobilise the excess dextrose which is then promptly removed from the blood stream If for some reason excessive amounts of insulin are produced in the body too much dextrose will be mobilised and removed from the blood stream, nervousness hunger and fatigue then appear If the blood sugar falls below 0 07 per cent these symptoms become accentuated until at about 0 04 per cent death takes place. Conversely, if insulin production in *the body is* deficient the blood sugar will not be mobilized and utilised by the body at the normal rate and hyperglycemia will result

Epinephrine or adrenalin and suprarenin, also play an important part in blood sugar *regulation The physiological action of epinephrine is antagonistic to* that of insulin, it has a depressor action upon the utilisation of dextrose by the tissues

The pituitary hormone resembles epinephrine in its effect upon carbohydrate metabolism Its excess often produces hyperglycemia and diminished dextrose tolerance of the body The exact mechanism of action is *not fully known* but it is believed it acts as a stimulus to the adrenal glands and does not influence the blood sugar directly

Thyroxin the hormone of the thyroid gland reduces the dextrose tolerance of the body It causes the glycogen content of the liver to diminish gradually, perhaps through,

stimulation of glycolysis. As in the case of pituitrin, it has been suggested that the effect of thyroxin is indirect and takes place through the *intermediary of adrenal glands.*

(2) Modes of Administration

Oral administration

Dextrose may be introduced into the human body by mouth or *per rectum* and parenterally by subcutaneous, intraperitoneal, intramuscular or intravenous injection. The most natural and common route *is by mouth. It is the most convenient since absolute* purity and exact dosage and concentration are unnecessary. As much as 1 lb may be ingested per diem without any harmful effects. The oral administration is indicated where dextrose serves as a food and source of quick energy and where a specific effect upon the alimentary tract is desired. It may be usefully combined with fruit juices or extracts

Rectal administration

...dextrose is controversial despite its ... administration the solution should ... Such solutions are least irritating ... be administered slowly to eliminate ... *es of 3-5 per cent dextrose solution* ... drip method. Other substances as

Parenteral medication

The injection of dextrose permits the direct introduction of an immediate source of energy into the tissues or blood stream. When dextrose therapy was first developed, reactions characterised by chills and fever occured occasionally. To-day however, reactions following the parenteral administration of dextrose are rare. The impurity of the ingredients of the infusion mixture is found to be responsible for the greatest number of reactions. The water fraction was recently shown to be the most consistent cause of reactions. *The solutions should be prepared in pyrogen free water and then sterilised.* All coloured, opaque or crystallised solutions should be discarded.

... The most suitable sites ... upper and outer parts of ... t irritating although some ... nt solution. Subcutaneous ... *of an excessive rate in* ... ypodermoclysis is an effec- ... f diseases of infancy and

Intraperitoneal administration.—The injection of dextrose solution into the peritonium is an excellent ... te being the line below the ... greater concentration tend ... e possibility of distension. ... sion is very rapid

Intramuscular administration.—The lateral and anterolateral surfaces of the thighs are preferable to the buttocks both may be used. The quantity of solution to be injected varies with each case depending upon distension of the muscles about the site of the injection. Infants usually take 20 to 40 ccm of a 10 per cent dextrose solution with ease, older children and adults up to 100 ccm at a time. Unlike hypodermoclysis the intramuscular *injection is usually not painful and is applicable to adults as well as infants* and children

Intravenous administration.—The intravenous injection of dextrose solutions is also an excellent means of administering specific drugs which cannot be introduced into the body by another route. However perfect asepsis an assembled apparatus and skill in the technique of administration are essential for good results. Intravenous dextrose may be given *either intermittently or continuously. The intermittent intravenous* administration of dextrose is best performed at the veins of the elbows and ankles in adults. In infants and young children the superior longitudinal sinus and the veins in the scalp are preferred. The solution must be maintained approximately at 37°C. The intermittent method is advantageous in the treatment of conditions in which osmotic pressure relations are involved (promotion of diuresis restoration of peripheral circulation, etc.) The continuous method, on the other hand is preferable when body fluids must be restored. *In the intermittent method 300 ccm at time of a 25 per cent dextrose solution may be*

given at the rate of 4 ccm per minute This is repeated as often as necessary blood sugar levels and clinical condition of the patient serving as guides to the number of injection

(3) Glucose in Therapy

There are few conditions in medicine and surgery in which glucose cannot be used with considerable advantage to the patient It should however be used rationally and method of its administration should be carefully considered with due regard to the patient s condition If possible oral route should be used but where this is not feasible it should be given by hypodermoclysis intramuscularly or intravenously as occasion demands and in proper concentrations If necessary it should be combined with insulin so as to ensure its assimilation by the tissues Hypertonic solutions up to 50 per cent in strength can be given intravenously with a view to remove collections of fluids from the body by diuresis Such solutions are also used to relieve arterial hypertension and increased cerebrospinal tension If intravenous injection have to be used glucose used should be pure and it should be dissolved in pyrogen free double-distilled water

In Surgery administration of glucose helps in stocking the liver with glycogen and in this way the toxic effects of the anaesthetic are minimised Some surgeons give intravenous injections of glucose starting a day or two before the operation Glucose administration is particularly useful in operations on the gastro intestinal and urinary tracts and such conditions where nourishment by the mouth cannot be given

tina' Glucose (dextrose) is useful in a large number of diseased conditions It can be given with benefit in cases of severe vomiting and diarrhoea either by the mouth or by the parenteral route whichever is feasible In peptic ulcer glucose given by the mouth is considered by some to have a neutralizing effect on the acidity of the stomach contents It is also believed to directly reduce hyper acidity by stimulating the secretion of insulin which is said to inhibit the secretion of gastric juice It would also provide the much needed nutrition to the muscle tissues Glucose requires no digestion and therefore is not irritating The motility of the stomach is said to be reduced

In coeliac disease in children subcutaneous injections of glucose with insulin may counteract faulty carbohydrate metabolism and thus improve the disordered fat metabolism

In most liver diseases the glycogen contents of the organ is on the low side, administration of glucose will help in replacing the depleted stock of glycogen and in this way combat the accompanying hypoglycaemia

In deficiency diseases there is a chronic condition of starvation of the tissues and glucose gives good results administered if necessary with insulin and deficient vitamins It is particularly useful in marasmus in children and conditions of malnutrition accompanied by diarrhoea As much as 250 gm may be given during the day

In cardio vascular disease especially when the heart is failing it may be life saving by supplying much needed nourishment to the myocardium

In allergic conditions there may be hypoglycaemia and consequently the glycogen content of the liver is reduced This decreases the resistence of the body and allergic conditions set in Glucose helps by stocking the liver with glycogen which counteracts this When given by the mouth it may

decrease putrefaction of proteins in the gut by bacterial organisms and in this way prevent their absorption into the circulation. Lactose is preferable in such conditions

Infectious and other serious conditions

In infectious disease the toxins produced give rise to increase in the metabolism in the tissues As digestion is often disturbed the absorption of nutritive substances from the gastro-intestinal tract is inhibited In such conditions glucose given by the mouth (it needs no digestion) is absorbed and thus prevent tissue breakdown If it cannot be taken by the mouth adequate quantities may be given by the parenteral route In such disease as pneumonia smallpox cerebrospinal fever and other serious infections it may be a life saving factor As much as 600 gm may be given either by the mouth or by injection (equalling about 2400 calories) In diphtheria it may be combined with serum treatment. In cholera 5 per cent glucose along with saline is useful in stimulating diuresis In tetanus a 25 per cent solution may be combined with magnesium sulphate solution (25 per cent) and given intravenously In cases of tuberculosis it may supply much needed nourishment to the system There are in fact very few conditions both in medicine and surgery where it cannot be useful if given rationally

In blackwater fever its use is the most essential part of the treatment In fact in almost all tropical diseases glucose can be used with advantage

to the portion of the fat with low melting point and is not destroyed by steam In ghee it is destroyed at the frying temperature of 200°C

Vitamin A has been concentrated into a fraction of the unsaponifiable lipoids of cod liver oil It is believed that it is a labile oxidation product of oxycholesterol

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few hours by th
vitamin A deficiency and if treated early will prevent degenerative changes in epithelial tissues As the trouble progresses, opaque spots are seen on the sclera, then there is con junctivitis and blepharitis and if not checked ulceration of the cornea occurs leading to blindness Famine and industrial depression bring the disease to light In extreme cases the skin becomes thickened and epithelium of the upper respiratory tract may be similarly affected

Vitamin A deficiency can be recognized by (1) measuring dark adaptation and (2) by estimating it in the blood This vitamin is necessary for maintaining the structure of body cells and its plentiful supply increases longevity and delays senility The effects of deficiency are seen in all the epithelial surfaces of the body (skin and mucous membrane) thers Changes are not pronounced as a rule in glands, affected It is essential for urinary secretion and stimulates the convers on of carotene to vitamin A eneration of the nervous system and it has been of lathyrism, other effects are respiratory infection

Although as much as up to 200 I U per kilo are sometimes given few untoward effects ice decreased resistance to is) In this condition the undice) and is sometimes

It is not correct to say that the administration of vitamin A reduces the liability to respiratory infection No relation between vitamin A and the resistance of the body to infection has been demonstrated, 600 I U represents the maximum daily requirements in man infants require as much as adults. The richest sources are halibut or shark liver oils, which are given in doses of a few grams The blood content of vitamin A can be estimated and vitamin A deficiency readily detected It is raised in conditions where storage capacity is defective resulting in carotinaemia.

When arsenic or antimony trichloride is added to an oil containing vitamin A a blue colour is produced and the intensity of the colour is roughly proportional to the vitamin A content This test provides a simple and rapid method for the approximate estimation of the vitamin A content of fats and oil and obviates the necessity for the biological test which requires 8 10 weeks The absorption spectrum of the colour produced in this test has been determined

Biological estimation of vitamin A is based on growth response of young rats The diet given to them contains all essentials except vitamin A so that arrest and resumption of growth can be attributed with certainty to the vitamin content alone

The following tests are also used —

(1) By Photometer —The eye is exposed to bright light so that visual purple is extinguished and the patient is shown small test spots of ble as the llows the ients can

100 ccm

(2) By Blood examination —For norma though it tends to be low in early spring The method employed is based on trichloride of antimony colour reaction and matching the depth of the colour of carotene against solutions of potassium bichromate or coloured glasses The process is assisted by the photocolorimetric method.

Carotene is useless to the body unless converted to vitamin A, its estimation in the blood is, therefore, of little clinical value

Shark Liver Oil

During recent years, a great deal of interest has centred round the production of shark-liver oil especially on the West Coast of India The fish liver oil is no stranger to India About eight decades ago India exported quite large quantities to the West Calicut being a big centre of production Around 1870, the price of cod liver oil fell below that of the Malabar fish oil and the Indian Industry practically died out for want of a suitable market Cod liver oil from Norway and other countries began actually appearing on the Indian market in increasing quantities and the country became more and more
... Norway in World War II, followed
rom the rest of the World The
ds of the other nations kept India
ıds of the civil population and the
Vitamin A, became quite consider
this stress, the Malabar fish liver

The high Vitamin content

It was soon established that the liver oil from the shark and the saw fish has a much higher Vitamin A potency than cod liver oil Occasional samples have potencies of several hundred thousand International units per gram, i e, well over 100 times the potency of standard Norwegian cod liver oil The average potency is however, of a lower order though still distinctly higher than that of cod liver oil In some areas, an average of
... the average Genuine
A minimum potency
ndum to the British
oil of this standard
oil

Deficiency in India

According to the latest International standard, the average daily requirement of an adult would be about 5000 units of Vitamin A The majority of people in India get very much less than this quantity in their food and for this the symptoms of deficiency are commonly met with among poorer classes A large section of the population would
...

is generally recognised that there is more extensive dificiency of Vitamin A than that of any other vitamin in India
... ment
s per
esent
llons

Supplement with Vit

The cod liver oil is naturally rich in Vitamin D In that oil vitamins A & D are so proportioned that no fur ... shark-liver oil, vitamin A is very predomi ... will be needed to render it more balance ... tions like calci ferol are easily available ... be difficult to supplement shark liver oil ... idering the im portance and the inter rel ... should be made a state policy to insist or ... amin D before marketing

During the first few years of the shark liver oil industry it was considered desirable and necessary to dilute the vitamin A content to the same level as in cod liver oil Groundnut oil was largely used for this purpose This practice led to a number of secondary difficulties It also facilitated the marketing of a number of spurious products. Even when used in drops any fish liver oil has a disagreeable smell Several ingenious methods for taking such oils along with food have been suggested but even then, the more fastidi ous people cannot miss the smell It has been suggested therefore that the vitamin in the oil should be concentrated free from smell Vitamin in the shark liver oil has been concentrated by molecular distillation and chemical method in Haffkine Institute Bombay and odourless and good tasting tablets have been prepared with chocolate base These are absolutely odourless and quite pleasant to taste These tablets are being now turned out in millions and are being issued to the people

2. The Vitamin B Complex

This group is now shown to consist of two factors one thermolabile and the other thermostable It contains a number of distinct principles B_1 or Aneurine or Thiamine, B_2 or Riboflavin Nicotinic acid or Niacin B_6 or rat anti dermatitis factor or adermin

Other allied vitamins are *Vitamin H* or Biotin which is shown to be a cyclic urea compound containing sulphur with carboxyl group It occurs in high concentration in tumours

Choline is present in B group and maintains normal kidney structure

Adenylic acid (a complex of adenin ribose and phosphoric acid) occuring in yeast is a respiratory mediator concerned with oxidation reduction mechanism in body cells

Pantothenic acid is a filterate factor necessary for growth in rats and an anti dermatitis factor in chicks but its role in man is not known In beriberi its blood level is 20 to 50 per cent below normal

(1) Vitamin B_1 (Aneurine, Thiamin)

Aneurine hydrochloride B P (thiamine hydrochloride U S P) was formerly known as *vitamin* B_1
containing vitan
pure state by e
stable at 100°C
vegetable but p

Aneurine is incapable of being synthesised by animal organism and animal tissues can store only very small quantities In vegetables it is found in the embryo of plants just under the husk in the grain of cereals such as wheat and rice, and also in nuts and seeds such as peas and beans In the process of milling or polishing of wheat and rice however the embryo and therefore most of the aneurine is removed leaving mainly the *starch store of the grain behind Malt and yeast are rich sources* but alcoholic beverages prepared from malt and yeast are almost devoid of aneurine The yeast cells being unable to synthesize aneurine, use up all the store present in malt during their multiplication

Almost all fresh vegetables and animal foodstuffs such as milk meat eggs fruit etc., contain some aneurine and this deficiency *is rarely met with except in populations* existing solely on a diet of polished rice

Aneurine is readily absorbed and stored in the tissues particularly in the liver kidneys and muscles it is abundant in heart Man can store considerable quantities as beri beri does not develop till after two or three months on a diet deficient in aneurine The explanation of the rarity of mental changes in beriberi as contrasted with the severity and frequency of peripheral neuritis is to be found in the fact that the brain tissue retains its store of aneurine more tenaciously than other tissues Prolonged diarrhœa interferes with the absorption of aneurine.

Subcutaneous injection of 50-500
intake by
of great
peutic use
absorbed
digestive
quantities

Aneurine is essential for proper carbohydrate metabolism, and is necessary to all ... bon dioxide and water ... yruvic acid Aneurine

def
adc
con
of
and it is probable ...
power of tissue respiration
peripheral nerves in beriber

Aneurine deficiency in non rice eating communities

Only the rice eating peoples suffer from beriberi Even with the poorest diets in other peoples, beriberi does not develop There are several conditions, however under which even well to-do people may develop aneurine deficiency (1) Diminished absorption of food associated with many chronic gastro-intestinal diseases, such as pyloric stenosis, chronic ulcerative colitis (2) In chronic alcoholism, subjects may drink very large quantities of alcoholic drinks such as beer, and may lose their appetite for fresh foods The increased intake of carbohydrate also leads to increased demands for aneurine thus aggravating the deficiency of the diet. A proportion of chronic alcoholics certainly do develop aneurine deficiency resulting in alcoholic heart disease and peripheral neuritis. These changes are often accompanied by mental changes (Korsakoffs syndrome) and it has been claimed that these changes are cured by nicotinic acid.

Symptoms and signs of moderate deficiency—Occuring chiefly in adults the following symptoms are common distaste for food unwillingness to consume a full diet, postprandial distension, digestive disturbances, neurasthenia, lassitude, skin dysaesthesias and calf muscle tenderness.

Symptoms and signs of severe deficiency—The following are the specific deficiencies benefitted by Thiamine (B_1) administration

Beri-beri—severe anorexia, polyneuritis serous effusion, subcutaneous œdema, and cardiac insufficiency

Alcoholic neuritis—with its attendant excruciating limb pains

Neuritis of pellagra—although niacinamide is the specific treatment for pellagra pain numbness, and other neurologic signs are relieved by thiamine (B_1)

Neuritis of pregnancy—the symptoms of peripheral neuritis late in pregnancy are frequently alleviated by vitamin B_1

Deficiency induced by excessive metabolism—unless adequate supplies of thiamine are administered, high fever, an elevated basal metabolic rate (thyrotoxicosis, heavy muscular work), excessive sweating and even intravenous glucose solution, may induce this deficiency

Psychic changes—negativism, general mental depression

Tests for aneurine deficiency

Two colour tests can be used [illegible]
cases of suspected deficiency (i) [illegible]
ferricyanide in an alkaline mediu[illegible]
(ii) *The formaldehyde azo test* [illegible]
the blood is also an indication of [illegible]
rats put on a B_1 deficient diet loose weight and heart beats come down from 500 to 550 per minute to 350. (iv) *Phycomycetes test* Growth of the mould *P blakesleeanus* is proportional to the concentration of B_1 in the medium It is used in the estimation of B_1 in whole blood, plasma, urine and cerebrospinal fluid

Normal requirements

The daily average requirement for an adult is about 1 mgm, infants require about one quarter of this amount, and the requirements in pregnancy and lactation are five times the normal adult average In pregnancy large amounts of aneurine are required and it is believed that the polyneuritis of pregnancy is a result of aneurine deficiency

Increased physical work, pregnancy and hyperthyroidism necessitates increased intake as the utilization of aneurine is directly related to that of carbohydrates

The international unit is the antineuritic activity of 3 gamma of pure B i e 300 I U = 1 mgm The minimum daily requirements for an adult of 70 kilo weight (11 st) on 3000 calories a day is approximately 300 I U or 1 mgm, but 500 to 700 I U is desirable Infants need 50-60 I U (0.2 gm)

Dosage and therapeutic us

In deficiency states 2 to 4 mgm are usually required to secure rapid improvement However, in doubtful cases large doses 10 to 20 mgm may be given for a week before the therapeutic test is held to be negative Aneurine should be given to all cases of alcoholic peripheral neuritis and heart failure It should also be tried in all cases of peripheral neuritis and myocardial weaknesses of obscure origin.

Aneurine hydrochloride is obtinable in tablets and in sterile aqueous solution in ampoules The hypodermic route should be used for administration in cases where the deficiency is due to defective absorption as in pyloric stenoses or chronic diarrhoeas. Where there is loss

of appetite and defective tone of the gastro intestinal tract, the parenteral route is also advisable In other cases it can be given by the oral route

No evidence has been brought forward to show that over dosage produces any ill effects

Diets deficient in one vitamin are often deficient in others Test administration of one of the B group of vitamins gives more accurate information for diagnostic purposes than giving of foodstuffs rich in all members of this group If deficiency of one member of this group is demonstrated it may be assumed that deficiency of the others either exists or is near at hand, and the proper treatment would be to provide all the vitamins in abundance

(2) Vitamin B_2 (Riboflavin)

Vitamin B_2 (Riboflavin) is also known as lactoflavin, Vitamin G It crystalizes in yellowish brown needles with no sharp melting point, its solubility is slight (2 5 part per thousand at 25°C) It is soluble in fat solvents and is stable in strongly acid solution and unstable in alkalies when exposed to light or irradiation with ultraviolet light It should, therefore, be stored in amber coloured ampoules

This vitamin is widely distributed in plants and animals milk, yeast fish roe kidney, liver and leafy vegetables being the best source It is heat stable and is not destroyed unless the medium is alkaline It occurs in yellow pigment of tubercle bacillus Its formula is 6 7 dimethyl-9 (d 1 ribityl) isoalloxazine The Bourquin sherman unit is equivalent to 2-2 5 microgrammes of pure riboflavin

Riboflavin plays an important part in metabolism forming part of a complex enzyme system concerned in oxidation reduction processes in living cells It aids the oxidation of carbohydrates, amino acids, lactic acid and aldehydes

Symptoms and signs of moderate deficiency are vague probably including lowered general health and retarded growth A tendency to seborrhoeic dermatitis episodes may appe ... al of the following signs may appear, (*a*) ... d mouth or other apertures, (*b*) *glossitis* with ... (*c*) *seborrhoeic dermatitis* chiefly of the face ... hobia, dimness of vision and accomodation defec ... and malaise

Most animals and men cannot synthesize this vitamin and it must be obtained from the diet In animals kept on riboflavin free diet conjunctivitis and keratitis are produced due to defective metabolism in the cornea and lens Vascularisation of cornea is a reliable early sign of deficiency, there is marked proliferation and enlargement of limbic plexus The ocular lesions are cured by riboflavin therapy, photophobia and itching respond within 48 hours with doses of 5 to 15 mgm and resolution of keratitis takes place later Acne rosacea and associated keratitis are examples of ariboflavinosis and curable with riboflavin Cheilosis and pallor of mucosa at the angles of the mouth eventually giving rise to transverse fissure extending downwards from the angles of the mouth is also due to ariboflavinosis

Riboflavin is absorbed from the intestines and its absorption is delayed in certain gastro intestinal diseases If intake is increased the amount stored in the liver is increased slightly It is excreted in urine as riboflavin

450 units (0 9 to 1 2 mgm) daily by boys and girls under 6 and 7 years 7 to 10 years require 540 units (1 08 to 1 32 mgm) and adults require 600 units or (1 2 to 2 5 mgm)

(3) Nicotinic Acid (Niacin)

Nicotinic acid amide was known as the pellagra preventing factor (P P factor) and is prepared by the oxidation of nicotine or by laboratory synthesis It is *B pyridine B carboxylic aci* ...

Nicotinic acid ...
and alcohol It ...
to air, cooking ...
it forms salts ...
to be actively ...
eggs fish and ce ...
acid is an esser ...

for the transfer of hydrogen in the oxidation processes of body tissues It has been also shown that inhibition of the activity of these enzymes in brain tissue may be produced by narcotic drugs and it is possible that the cerebral disorders and tissue changes in pellagra may be due to lack of nicotinic acid amide, and consequent lack of co-dehydrogenases.

Estimation

Nicotinic acid is estimated by colour test with 2.4 dinitrochlorobenzene, also with cyanogen bromide and aniline In the blood it is estimated by growth promoting actions on various micro-organisms Biologically it is estimated by its cure of 'black tongue' in dogs

Nicotinic acid contents of most food varies from 1 to 100 mgm per 100 gm of material and certain crude liver extract may contain as much as 200 to 300 mgm per 100 gm

Vasodilator action.

Toxic effects are produced by over dosage of nicotinic acid in animals rarely in man, the amide is better tolerated It has a vasodilator action and produces flushing of the face and neck, sensation of heat itching and tingling which pass off in half an hour Throbbing headache, nausea vomiting and transient abdominal pain, urticaria, cyanosis may occur Nicotinic acid given intravenously produces increased flow of blood in brain in man without any change in blood pressure In doses of 100 mgm orally it always produces slight flushing and fall of blood pressure in doses of 30 mgm it may also do so Slight increase in gastric and intestinal mobility may produce a transient general vasodilator effect It is stated that nicotinic acid amide does not produce any of the minor unpleasant effects associated with administration of nicotinic acid.

Absorption an[d] excretion.

Nicotinic acid is absorbed from the intestine and in disease of the gastro-intestinal tract this may be interfered with and lead to deficiency It is probably stored in the liver and in pellagra the liver is damaged and liver extract is effective in this condition [illegible] is deficient [illegible] art being in [illegible] r the amide [illegible] ted in urine partly as such and partly as trigonellur

Deficiency symptoms

Symptoms and signs of moderate deficiency are the pre pellagrous state, which is not well defined, but mental depression gastro-intestinal disturbances, dermatitis, and glossitis in mild form are likely to appear The evidences of deficiency are closely similar at all ages That of severe deficiency is manifested by the disease known as pellagra The symptoms and signs include gastrointestinal dysfunction exfoliative glossitis together with red purplish appearance of the tongue, exfoliative dermatitis of the arms and legs profound mental depression, and frequently additional signs and symptoms of riboflavin and thiamine deficiency

Alcoholic dementia.

Alcoholic dementia and mental disturbances occurring as a result of chronic gastro-intestinal disease, may be the result of nicotinic acid deficiency often accompanied by aneurine deficiency as well Prolonged previous treatment with bromides in such cases may delay mental improvement due to retention of bromine in the tissues, and this factor should be borne in mind when evaluating the success of treatment with nicotinic acid

No simple specific test is so far available for nicotinic acid deficiency, but trial treatment and estimation of co-dehydrogenase in blood and urine can be carried out.

The daily requirement in man is 30 to 60 mgm, minimal requirement to prevent pellagra is 8 to 16.5 mgm (0.12 mgm per kilo) daily

Administration

The normal human requirement or protective dose is not known. In the treatment of pellagra the effective oral dose is about 500 mgm daily In order to avoid unpleasant side effects [illegible] naller doses of 50 mgm [illegible] ose may be reduced to [illegible] uced to 100 mgm daily [illegible] ssitis, sprue and allied [illegible] hosis due to defective [illegible] 150 mgm.

(4) Vitamin B_6 (Pyridoxin, Adermin)

It was isolated in 1938 and it forms one fraction of the factor originally known as vitamin B_2 complex It occurs naturally in cereals, egg yolk, liver seeds, rice, etc., and can also be synthesized

The chemical formula for pyridoxine is 2 methyl 3 hydroxyl 4 5 dihydroxy methyl pyridine It is a white crystalline powder with a bitter taste and melting point 157° to 160°C

Lack of this vitamin in the diet is the cause of "rat acrodynia" characterized by dermatitis of the paws nose and ears. Many investigators have reported B_6 necessary for growth in chicks This vitamin probably assists in the metabolism of unsaturated fatty acids Recent evidence has indicated that when equal doses of pyridoxine hydrochloride and thiamine hydrochloride are administered in substantial therapeutic dosage by mouth many cases of hyperemesis gravidarum are relieved of their excessive nausea and vomiting

Chick cleared up the confusion regarding the dermatitis syndrome of pyridoxine deficiency and showed that rats deprived of vitamin B_6 developed typical dermatitis and were cured when fed on pure vitamin B_6 It has also been shown that after treatment of typical pellagra with thiamin and nicotinic acid the symptoms of insomnia irritability, weakness etc are removed by administration of pyridoxine, in 50 mgm doses intravenously It has been used in the treatment of pseudo-hypertrophic muscular dystrophy, in Parkinsonism arsenical peripheral neuritis and chorea It is useful in angular stomatitis

(5) Folic Acid

Introductory and General—The name folic acid was originally given to an almost pure chemical substance isolated from spinach, it is found in many other green leaves including grass and in mushrooms, liver, and yeast. Folic acid will take its place among the vitamins, it has many natural sources and exists in several, probably closely related forms in the same way as vitamins The folic acid compounds have been studied under several names, and the following are now known to be folic acid variants—vitamin M, deficiency of which causes a pellagrous syndrome of anæmia, leucopenia, diarrhoea, and mouth lesions in monkeys, vitamin B_c deficiency of which causes a nutritional anæmia in chicks, vitamins B_{10} and B_{11}, responsible for growth and feather development in chicks, and the "eluate factor" (from liver) and the "*L casei* factor," both essential for the growth of *Lactobacillus casei* and *Streptococcus faecalis* R The *L casei* factor from liver has been synthesized and its constitutional formula has been established, the name "pteroyl glutamic acid" has been suggested for this folic acid compound which will so far as is known, produce all the effects of the other forms The *L casei* factor from yeast differs only in the number of glutamic acid molecules Folic acid appears to be distinct from the hæmopoietic principle of the liver. It is also distinct from the primary factor which is the liver fraction active in very small amounts especially in the presence of accessary substances (Jacobsan & Subba Raw, 1937)

Chemistry.—Similarities between properties and activities of *L casei* factor and folic acid were observed by many workers and Subba Raw et al (1945) synthesised folic acid identical with the natural *L casei* from liver Angier and his colleagues (1946) have worked out the structure of liver *L casei* factor or folic acid and have described two methods of preparing it It is a compound of p aminobenzoyl 1 (+) glutamic acid and a pteridine 2-amino 4 hydroxy-6 methyl pteridine, the linkage is through the 6-methyl group

The more interesting of the two methods of preparation utilises glutamic acid p-aminobenzoyl chloride and propionic aldehyde all of which are normal laboratory reagents and 2 4 5 triamino-6 hydroxy pyrimidine, which should not present any special difficulty in preparation, the yield is 15 per cent

Folic acid is not claimed to be the liver principle, it is a bright yellow crystaline substance, whereas the most active liver preparations effective in pernicious anæmia are now colourless The results with thymine suggest that folic acid probably acts as an enzyme or co enzyme which sets in motion the system for the production of the liver principle Meanwhile here is a single substance of known composition which is therapeutically active in many macrocytic anæmias

Deficiency symptoms

Symptoms and signs of severe deficiency in adults are macrocytic anæmia of sprue macrocytic anæmia of pregnancy, macrocytic anæmia accompanying pellagra, macrocytic anæmia of gastro-intestinal origin, pernicious anæmia, and in infants—macrocytic anæmia of infancy.

Experimental work—Folic acid is widely distributed in nature and is present in any mixed diet, natural folic acid deficiency in man has not been described, though deficiences have been experimentally produced by giving specially purified diets. Rats and probably other mammals are not dependent on food intake for their supplies of folic acid, since, as with vitamin A, they can synthesize it in their intestine. The addition to the diet of a sterilizing sulphonamide like sulphasuxidine prevents such synthesis, and this was how Nelson and Elvehjem produced the folic acid deficiency syndrome in rats. This syndnome consisted of granulocytopenia and lack of growth and was corrected by administration of folic acid concentrates Leucopenia especially lack of poly morphonuclears, is the outstanding hæmatological effect of artificial folic acid deficiency in monkeys and rats In nutritional anæmia in man administration of folic acid not only corrects leucopenia but its effects in improving the anæmic condition are even more powerful

Some animal experiments on folic acid deficiency have been carried out by Endicott and colleagues They fed rats on the usual purified diet to which all vitamin B factors except folic acid had been added, together with succinyl sulphathiazole to prevent synthesis in the bowel The bone marrow of these animals became hypocellular, the granular leucocytes being most affected, and the erythropoietic tissues were also depleted The rats developed a severe leucopenia, but only some showed anæmia which was not of the macrocytic type as expected, but of normocytic type Administration of crystalline folic acid caused a rapid regeneration of the bone marrow with a well marked proliferation of the granular leucocytes. In the anæmic rats there was also a temporary hyperplasia of the erythropoietic tissues These findings, though they bear little relation to the human conditions bene fitted by folic acid, confirm its connection with blood-cell formation and are likely to stimulate further studies of its effect in granulopenia

The value of synthetic folic acid in certain types of anæmias and diarrhoeas was demonstrated by Spies in a number of cases of pernicious anæmia, nutritional macrocytic anæmia, sprue and in some other miscellaneous cases The criteria of diagnosis were

though the fat content of the stools remained high, the fat glucose tolerance curves returned towards normal and the patients put on weight. One of these patients had previously received other vitamin B factor nicotinic acid, riboflavine pantothenic acid, and pyridoxine for five weeks without effect

Zuelzer and Ogden in a report on a group of severe megaloblastic anæmias in infants from birth to sixteen months of age treated some of the patients with intramuscular liver extract and the others with folic acid. The results were comparable, there was a definite reticulocyte response a sustained rise in the red-cell count and hæmoglobin, and transformation of the megaloblastic to a normoblastic marrow Carruthers gave folic acid to six patients with chronic diarrhœa and an iron-deficiency type of anæmia, the diarrhœa was rapidly checked but the anæmia was unaffected

There is thus a considerable body of evidence that folic acid is effective in the treat ment of sprue and nutritional macrocytic anæmia

Therapeutic uses and dosage—Folic acid is useful in pernicious anæmia nutritional macrocytic anæmia pellagra sprue and macrocytic anæmia of pregnancy The dosage of synthetic folic acid is being rapidly worked out It can be given by mouth or parenterally dissolved in disodium phosphate For *pernicious anæmia the oral* route is adequate, 20 mgm is given daily in the relapse phase and this dose is maintained until remission is well established when it is reduced to 10 mg daily or less Doan and Davidson and Girwood, report suboptimal results with doses of 2 10 mg daily For maintenance Doan reports that the dose needed varies from 40 mgm a week to 20 mgm every third week, with this regime minor neurological signs improve and no case has so far developed signs of involvement of the spinal cord tracts Good results have been reported with single large doses of 150 mgm parenterally or 400 mgm by mouth they produce a rapid reticulocytosis but are probably unnecessarily large In nutritional anæmias 20 mgm daily seem adequate and the same dose is effective in sprue the parenteral route has some advantage in the early part of the illness The general conclusion is that 30 mgm is an effective daily dose for these anæmias and larger doses should not be given, folic acid is not easy to prepare and supplies are unlikely to be plentiful for some time In the refractory types larger doses may be in order, but little information is yet available according to Doan the maximal permissible intravenous dose is 150 mgm since larger doses may cause histamine like vasomotor disturbances Doses up to 400 mgm have been given by mouth without distress

A comprehensive review of the development of knowledge about folic acid *has been published by Berry and Spies and another appears in the UNRRA* Bulletin The later remarks that folic acid is valuable in the treatment of anæmia, particularly macrocytic anæmia irrespective of the clinical classification The evidence so far suggests that a response from folic acid can only be expected in patients whose sternal bone marrow reveals definite megaloblastic *change and classification on these lines has in fact* been followed by all clinical workers with folic acid In nutritional anæmias this classification is particularly necessary since non megaloblastic macrocytic anæmias are common and there is no evidence that they respond to folic acid

(6) Other Vitamins of the B Group

(1) *Vitamin B_3*—This vitamin has been shown to be essential for the growth of pigeons This thermolab le factor occurs in dried yeast and wheat embryo but has not been isolated It may be identical with pantothenic acid

(2) *Vitamin B_4*—A specific type of paralysis in rats and ch cks results from the lack *of this vitamin* the existence of which however is doubtful This may be identical with other known factors Recent work identifies it with the aminoacids arginine and cystine

(3) *Vitamin B_5*—This alkali heat stable water soluble factor has been shown to be essential for the weight maintenance of pigeons Recent work however indentifies this with vitamin B_6 (Pyridoxine)

(4) *Vitamin B_7*—Pigeons develop digestive disturbances in the absence of this factor This is present in rice polishings but has never been isolated

(5) *Vitamin B_8 (Adenylic Acid)*—Adenylic Acid or Adenosine Monophosphate a complex of adenyne ribose and phosphoric acid is widely distributed in nature in cereals glandular tissues and yeast from which it can be extracted It is said to be essential for the phosphorylation of glucose adenylic acid being first converted into adenosine triphos phate which transfers its labile phosphate to glucose That the energy of muscular contract on is derived from the breakdown of adenocine triphosphate is supported by evidence this reaction being catal sed by calcium ions Ruskin reported success with iron adenylate in the treatment of agranulocytosis following chemotherapy It is stated that adenlic acid enhances the effect of vitamin B_1 in cases refractory to treatment with the latter alone Adenylic acid inhibits bacterial growth Sp es and collaborators reported that

adenylic acid has a powerful pharmacological action. Rapid clinical improvement has [illegible] on, pellagra and [illegible] quately to yeast [illegible] its status as a [illegible]

(6) *Vitamin B₁₀ and B₁₁*—These two chemically unidentified water-soluble members of the vitamin B complex are stated to be necessary for growth and proper feather development in the chick. These factors may be identical with vitamin Bc

(7) *Vitamin B_c*—Vitamin Bc, also known as the chick anti-anaemic factor, cures a condition of dietary deficiency in pigeons in which these refuse to grow and develop an [illegible]

with folic acid.

(8) [illegible]

has not been confirmed.

(9) *Vitamin M*—This vitamin is identical with folic acid, the deficiency of which is said to produce cytopoenia as well as lowered resistance of intestinal mucosa to infection by *B dysenteriae* in monkeys. Oral lesions resembling pellagra have also been observed consequent to lack of this vitamin in monkeys It is present in yeast and liver extract

(10) *Factor U*—A water soluble growth factor of chicks, it occurs in yeast, wheat, bran and corn This may be identical with vitamin Bc.

(11) *Rice Polish Factor*—A factor, recently discovered, it is essential for the growth and maintenance of animals receiving all other known vitamins or factors It is present in rice-polishings and has been suggested to be complementory to vitamin B₆ in preventing rat dermatitis This really may be a complex, as it can be replaced by a mixture of glycine and glycuronic acid or certain pentoses

(12) [illegible] "lipotropic factor" which prev[illegible] constituents of all plant and [illegible] y is not definitely known the [illegible] ntothenic acid, for normal gastro intestinal functions

A variety of pathological conditions have been suggested to be due to lack of this [illegible]

(13) *Choline*—Choline is essential for the metabolism of neutral fat as well as of cholesterol It is lipotropic and prevents deposition of excess fat in the liver of rats on a diet rich in fat The exact mechanism of this process in not known Deficiency of choline in the diet leads to the occurance of nodular cirrhosis of liver as also haemorrhagic degeneration of kidneys in some species It is also protective against liver damage by toxins such as, choloroform, in rats.

However, choline deficiency is unlikely to occur in man owing to wide distribution of this factor in animal and vegitable foods, egg yolk, nerve tissues, liver and wheat germ are rich sources of this vitamin, though it is also present in green and leguminious vegetables; milk is however not a rich source and the suggestion that a diet of cows' milk and a B coli infection may be responsible for infantile cirrhosis of liver, merits consideration

The importance of high protein diet in the treatment of hepatic lesions is suggested from recent clinical studies Choline is essential for certain other functions in animals such as, normal nutrition of the chick and for egg production, for the prevention of perosis or slipped tendon in the birds and for the lactation and normal nutrition of rats. In addition choline is utilised in the animal organism for the formation of acetylcholine. Choline require

ment of dog is about 35 mg/per kg of body weight daily that of chick is 75 mg/daily Generally speaking the young growing animal needs more of it than the adult Dogs made artificially diabetic have also been found to require choline

(14) *P—Amino Benzoic Acid*—It is a vitamin and has been shown to be necessary for

of pigmentation in vitiliginous patches *in depigmented areas in patients* with alopecia areata

(15) *Pantothenic Acid*—It is isolated from raw liver and possesses the property of *stimulating the growth of yeast and has been identified as the* 'chick anti dermatitis factor"

vitamin B complex and has been shown to have a synergistic effect in the human system in association with riboflavin Pantothenates have been employed in man but precise indications have not been determined

(16) *Biotin (Vitamin H, coer*
members of the vitamin B compl·
eggs and peas cocoa and cereals
staphylococcus, strains of clostridii
higher plants and a growth factor for the rat and most animal *If rats are given purified* diets containing sulphaguinidine or succinyl sulphathiazol which are bacteriostatic signs and symptoms of biotin deficiency are produced the effect being presumably due to interference with the bacterial synthesis of biotin in the intestines

3. Vitamin C. (Ascorbic Acid)

Vitamin C is ascorbic acid B P and is also known as hexuronic acid or cevitamic acid

It condenses with aldehydes ace ... the form of pale glass crystals
melting at 192°C When dry an
Autoclaving at 120°C for 20 minu
solutions of vitamin C can be stabi
as tartaric or citric acid Vitamin
an anti ascorbutic as ascorbic acid
of vitamin C=20 I U, but this standard is not now used

It is a colourless compound soluble in water and possesses marked reducing pro*perties It is easily* oxidized and can be converted back into ascorbic acid by reducing agents It probably plays an important part in transport of hydrogen in cell metabolism Deficiency of this substance causes scurvy

Ascorbic acid occurs in all growing vegetable tissues Green vegetables and fresh fruits (lemons oranges and other citrus fruit black and red currants strawberries cabbage tomatoes potatoes onions etc), contain large quantities of this vitamin and smaller quantities are contained in fresh meat and milk. Unripe seeds *e g* green peas contain ascorbic acid *which disappears when they ripen and dry but reappear when they* germinate It is present in many fruit juices and vegetables, but the amount rapidly decreases on storage, due to the presence of an oxydase enzyme in the plant juices Human milk contains 4 to 8 mgm per 100 ccm cows milk 1 to 2 6 mgm and pasteurised milk under 1 mgm The body can store ascorbic acid and depends for *its supply on* fresh vegetables This vitamin has been definitely proved to be a protective against scurvy

Ascorbic acid is very unstable and is destroyed on cooking or drying It is however, fairly stable in the rind of citrus fruits and in tomato juice *Ordinary cooking destroys* most of it in vegetables and the duration of the heating is more important than the

temperature to which they are raised Cabbage loses about 80 per cent of its ascorbic acid content by heating to 100°C for twenty minutes or by heating to 60°C for an hour Ascorbic acid of the citrus fruit and tomato is stable even on cooking

Scurvy

In scurvy osteoblast and odontoblast activity is normal and failure of connective tissue cells to form supporting tissues leads to thinning of bones and teeth. It is said that within twentyfour hours of administration of ascorbic acid improvement begins to take place. It is claimed that utilization of ascorbic acid is higher than normal during infective processes and that it may be of significance in resistance to bacterial infections In scurvy with severe anæmia reticulocyte crises ensue soon after administration of ascorbic acid suggesting that it may be an essential factor in hæmopoeisis Anæmia is frequently associated with scurvy and reacts well to ascorbic acid as do other forms of nutritional anæmias It is also essential for wound repair and is present in young granulation tissue and adjoining skin

In bacterial infections

There is some evidence that vitamin C has an effect on the production of anti bodies against bacterial infection. It also possesses bactericidal and bacteriostatic properties and inactivates certain toxins, such as *B dysenteriae Cl tetani* and *Cl oedematiens* It is also concerned with complement activity of serum.

Physiological action.

It is suggested that vitamin C is a component of a reversible oxidation reduction system acting as a hydrogen transporter or respiratory catalyst This vitamin is specially abundant in the corpus luteum the adrenals the pituitary gland and other glandular tissue It is said to stabilise the hormones and in scurvy symptoms resemble adrenal deficiency It may antagonize thyrotoxin

Administration by mouth has no effect on the blood sugar but intravenous injections lower it in normal persons Vitamin C is essential for synthetic processes within the cell It is absorbed by the intestines and if this is interfered with the diseased condition results This vitamin is stored in organs and tissues with high metabolic activity (adrenals are richest) Its blood range is 0·6 to 2·5 mgm

Excretion.

The bulk of vitamin C is excreted by the urine small quantities in sweat and fæces When the tissues are saturated with large doses the urinary excretion rises Daily excretion of 13 mgm is borderline between deficient and adequate intake.

Requirements in man

The indispensable minimum is 25 to 30 mgm per day (0.4 to 0.5 mgm per kilo), the optimum is 50 to 75 mgm daily but even larger quantities are needed during pregnancy and in acute infections. It should therefore, be regularly supplied, otherwise there is deficiency Boys up to 15 years require 90 mgm daily and adults 30-100 mgm

Tests

(1) [illegible]

(2) *Urinary excretion test.*—The amount of urine required to discharge the colour of a measured quantity of 2·6 dichlorophenolindophenol is determined. There are, however, substances in the urine which do this, *e g*, cysteine and thiosulphates. A similar test is used for its estimation in the serum.

(3) *Capillary fragility test*—A circular area 60 mm in diameter is marked off in the antecubital fossa and a blood pressure cuff is placed at least 2·5 cm above this Pressure is then pumped to 90 mm mercury and maintained for 15 minutes The pressure is then reduced and petechiae are counted The patient should not have a hot bath on the day of the test. Capillary fragility becomes pathological with blood values between 0.10 and 0.14 mgm per 100 ccm Value above 1.4 mgm per cent is the threshold value and corresponds to vitamin C saturation

Therapeutic uses.

In scurvy and diphtheria it is specially useful. It has also been used in pneumonia, tuberculosis, rheumatism typhoid malaria, dental and oral conditions hæmorrhagic diseases, pernicious anæmia, skin diseases and eye conditions

Most of the dietaries of the tropics are quite well supplied with anti scorbutic substances and therefore scurvy is seldom found in India.

The susceptibility to scurvy varies widely for different kinds of animals. Guinea pigs develop typical scurvy after 3 weeks without green food human beings take a much longer time to develop the disease Rats, mice cattle and fowl appear quite unsusceptible, apparently they are able to manufacture the vitamin (in their liver)

In infancy and pregnancy ascorbic acid deficiency may be corrected by giving ascorbic acid tablets The richest palatable source is fresh orange juice which contains 10 mgm per 100 ccm, tomatoes contain 13 to 39 mgm pen 100 ccm, apples contain little but cabbages, cauliflower and fresh potatoes are good sources

Probably less than 25 mgm of ascorbic acid per day is inadequate even for infants and an intake of at least 50 mgm should be aimed at in adults In the presence of bacterial infections 100 to 200 mgm, and during pregnancy 100 mgm is probably the minimum

The liver of infants at birth is rich in ascorbic acid, which becomes depleted if the child is breast fed more rapidly if fed on cows milk, and very rapidly if heated or preserved milk is given All active tissues contain ascorbic acid. Actively growing tumours are rich in it and its high utilization may possibly be the cause of purpura in these conditions

Plasma should contain 1 to 2 mgm per 100 ccm and in scurvy the value falls to 0 7 mgm or lower The urine contain at least 25 mgm in a 24 hour specimen, if less *is excreted its store is badly depleted.*

4. Vitamin D (Calciferol)

Vitamin D or the antirachitic or calcifying vitamin—Several substances have anti rachitic properties the important among these are —

Calciferol (Vitamin D_2) is manufactured artificially by 'activating' ergosterol, it does not occur naturally

Vitamin D_3 Sterol 7 dehydrocholesterol occurs naturally and is formed in the skin by the action of the sun Ergosterol is best irradiated in solution but if alcohol is used, there is liability of its being over irradiated and forming *toxisterol*

Calciferol is a white crystalline substance which is stable at room temperature but which loses its antirachitic properties at 18°C, it completely dissolves in oil at 80°C Biological assay is the only method of its estimation

In man vitamin D is derived from sunlight acting on the body In the absence of sunlight carbon arc or mercury vapour quartz lamp is an excellent medium for its production. Symptoms and signs of moderate deficiency are rarely detected in adults Probably an abnormal calcium phosphorus utilization occurs with possible additional dental and bony changes In infants and children fretfulness sweating constipation irregular and abnormal tooth and bone development and malaise accompanied by hypocalcaemia occur frequently Symptoms and signs of severe deficiency in adults are manifested by osteomalacia usually occuring in women and complicated by tetany and chronic diarrhoea Hypocalcaemia of parathyroid tetany is another sign of vitamin D lack The commonest ... bowed legs craniotabes malforma ... ifestations including ... amentous relaxation ... dental development.

Estimation is carried out by cure of rickets test Groups of rats are fed on a rachitogenic diet untill rickets develops To the diet of one group a standard vitamin D preparation is added The bone developed stained with silver nitrate appears as a black line In the bone ash method groups of rats are fed for 4 to 6 weeks with various levels of standard preparations under test They are then killed and the femoral bones are incinerated and the amount of calcification determined.

This vitamin is present in cod liver oil in relatively large quantities and also occurs in fish oils (e g salmon *herrings in Western countries hilsa king fish etc in India)* animal fats eggs and butter green leaves contain only small quantities It is now known that vitamin D is produced by the exposure of ergosterol to a special wave band of ultraviolet light. It may be produced artificially by such irradiation of the isolated ergos... ...which contain ergosterol It was noted that rickets could ... was soon found that exposure to sunlight ...s Antirachitic properties can be conferred ...nselves antirachitic by short exposure to ... principle or the provitamin D was indeed a sterol of an unsaturated and labile type of which *ergosterol is the only known* representative

Calciferol occurs in all tissues especially in the nervous system, skin and adrenals. It was originally produced from ergot and, therefore, called 'ergosterol but is now prepared almost exclusively from yeast.

5. Vitamin E

Vitamin E is known as alpha, beta or gamma tocopherol, the antisterility or antidystrophic vitamin, and has been synthesised, its deficiency, produces sterility in male rats, and failure in the female to carry pregnancy to term, and possibly in other [illegible] placenta and absorption of [illegible] Degeneration of peripheral [illegible] nental animals and that of [illegible] ficiency being the cause of habitual abortion in women has been considered and it has even been given clinical trials with doubtful results Wheat germ and green leafy vegetables (lettuce) are the only rich sources of vitamin E.

6. Vitamin K

[illegible]

Menaphthone B.P (*Menadione, vitamin K analogue*)—It is methyl naphthaquinone derivative It is a yellow powder and is sold under the proprietary name of kapilon and prokyavit in ampoules containing 5 mgm dissolved in 1 ccm of oil It should be given intramuscularly to ensure absorption oral administration is unreliable, but if given orally it should be combined with 2 to 3 gm of bile salt. The absorption of 5 mgm produces a prolongation of clotting time

It is useful in hæmorrhagic states of the new born. In surgical operations and cases of the obstructional jaundice of long duration where there is tendency to bleeding, one injection before operation may raise the clotting time to normal. In hæmophilia it is of no value but the administration of oestrogen, natural or synthetic, may check the bleeding Hæmorrhagic disease of infants may be prevented by giving vitamin K to mother just before delivery in doses of 1 mgm daily

7. Miscellaneous Vitamins

Vitamin F—[illegible] oleic, linoleic and arachidonic acid [illegible] s not clear whether it is a pure con[illegible] biotin etc., which also have this [illegible] large quantities in vegetable and seed fats though not in margarin, but the presence of arachidonic acid is doubt-

ful Deficiencies of vitamin F produce fat deficiency disease due to deficiences of the essential unsaturated fatty acids characterised by retarded and ultimately arrested growth accompanied by a raised metabolic rate altered fat and water metabolism, changes in the skin and hair renal degeneration and impairment of the sexual functions

Vitamin G—It was applied to niacin amide but now it is synonymous with riboflavin.

Vitamin P—It is also called *citrin* and is said to control capillary permeability and occurs in grapes grape juice, prunes and lemon juice It consists of two flavone glucosides (hesperidin and eriodictol) but has not yet been synthesized

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CHAPTER X

NUTRITIONAL DISEASES

INANITION AND ITS TREATMENT PROTEIN HYDROLYSATE RATIONALE OF THERAPY—NUTRITIONAL OEDEMA—EPIDEMIC DROPSY THEORIES OF CAUSATION AND CLINICAL ASPECTS, PROPHYLAXIS AND TREATMENT—BERI BERI THEORIES OF CAUSATION AND CLINICAL ASPECTS INFANTILE BERI BERI TREATMENT AND PROPHYLAXIS—PELLAGRA THEORIES OF CAUSATION AND CLINICAL ASPECTS PROPHYLAXIS AND TREATMENT—RICKETS AND OSTEOMALACIA TREATMENT—SCURVY—SPRUE CAUSATION AND CLINICAL ASPECTS TREATMENT—LATHYRISM

1. Inanition and its Treatment

Introductory—The diet of the people of India generally is very much on the low side and there are large tracts of the country where it borders on starvation Although the modern facilities with regard to transport of food grains and cereals have done much to improve the situation, famines not infrequently occur Famine on quite a large scale occurred in Bengal in 1943 when many millions of people died of starvation There is a large indigent population in the towns of India who live by begging and these are the unfortunate people who suffer most During the Bengal Famine of 1943 a large number of cases of starvation and inanition of extreme degree were brought to medical institutions for treatment The following account of diagnosis and treatment of such cases is abstracted from the report of the Committee of Enquiry into the effects of starvation set up by Research Fund Association (I.M G Feb 1944, P 74)

"The cases admitted to hospital from the 'sick destitutes' could be divided roughly into three groups—(*a*) those suffering from inanition due to starvation only, (*b*) those suffering from inanition due to a combination of starvation and disease, and (*c*) those showing relatively little inanition but suffering from acute disease. The methods of handling and management of these groups of cases therefore differ somewhat.

Diagnosis—"The diagnosis of inanition is comparatively easy The patient is usually very thin and weak and shows the characteristic mental picture of inanition, often a marked apathy The skin is dry and cold, all the organs and tissues are shrunken, the subcutaneous fat is completely absent the temperature is sub-normal systolic, diastolic and pulse pressures are reduced, The eyes are shrunken and there are frequently other signs of dehydration Often the wasting of the limbs is masked by the presence of œdema. (Care should be taken to make sure that this is not caused by nephritis) There is sometimes present a diarrhœa and colitis which may be neither bacillary nor amœbic.

"The diagnosis in patients of the second group those showing inanition plus disease, is often more difficult The predominating clinical picture is that of inanition and moreover the presence of d sease may be completely masked by the inanition. The patients will frequently show malarial parasites in the blood but have no temperature and show no splenic enlargement.

"Similarly in the presence of an infection which commonly causes high fever the temperature may be sub-normal, apparently as the result of inanition. In the same way cases of amœb c dysentery may show little diarrhœa and stools not typical of the disease. Such pat ents are frequently admitted to hospital and treated for inanition, and when the general condition begins to improve they develop the fever and other symptoms which are characteristic of the infection from which they are also suffering

"The diagnosis in patients of the third group presents no particular feature The patients, though weak are usually not collapsed, the pulse is good though often rapid, the body temperature is frequently raised, and the patients show the typical manifestations of the d seases from wh ch they are suffering The common diseases found have been malaria, mostly mal gnant, dysentery sometimes amoebic but more often bacillary pneumonia, nephritis, bronchitis, Naga Sore tuberculosis, anæmia, urinary tract infections, etc.

(1) Treatment

Treatment general—If the predominating clinical picture is that of disease then the emphasis should be laid on treatment for that disease but if as is usual the predominating clinical picture is that of inanition then the inanition should be treated first Many of the patients have been exposed to cold and have little or no clothing and a good supply of clothing blankets and bedding is essential The treatment of inanition and of the diseases frequently found in these sick destitutes is described below —

Dosage of drugs—In considering the treatment of these patients it should be remembered that the body weight of most of them is abnormally low and also that they are usually very weak The dosage of drugs therefore has to be planned accordingly In general the ordinary standard dosage of any drug should be halved and this principle been adopted throughout these notes

Treatment dietetic—Diet treatment in disease superimposed on starvation is important A healthy person suffering from acute infection may require little diet during treatment since he has adequate reserves A starved person suffering from acute infection has no reserves and the diet must be kept at the maximum possible level Only in inanition and severe gastro intestinal disorders should the diet be markedly restricted and then only for the minimum possible time A highly nutritious fluid diet is of vital importance in this work

Inanition—A considerable number of patients may be brought to hospital in a state of collapse

Treatment of collapse—The general treatment for collapse should be adopted—rest warmth warm fluids etc followed by a suitable diet but in severe cases intravenous therapy is strongly indicated and special preparations of protein hydrolysates containing vitamin B complex with glucose are being made available If this is not available or is contra indicated 5 per cent glucose saline may be given

Intravenous peptone glucose—Intravenous injections of peptone glucose are recommended for all advanced cases of starvation in a state of collapse (Cases of group I and sometimes of group III vide infra) The injections help to revive the cases quickly and enable them to take suitable diet by the mouth

Peptone glucose for injection is supplied in screw capped transfusion bottles It is a mixture of 5 per cent glucose 5 per cent protein hydrolysates and contains riboflavine nicotinic acid and thiamin It is of a clear port wine colour free from precipitate or turbidity Every batch before issue is tested bacteriologically for sterility immunologically for freedom from allergic reactions and pharmacologically for absence of toxicity

The quantity contained in each bottle is usually 200 ccm which represents the average dose for one injection for an adult Bottles containing 400 ccm are also supplied

The bottles are best stored in the dark in a cupboard at room temperature Storage tends to deepen the colour but this is of no consequence Bottles showing precipitate or turbidity or giving out a foul odour on opening should be rejected On opening the screw caps of good bottles a noise is heard due to the rushing of air into the vacumized bottles when the caps are found loose it is best to reject the bottles Once the cap is opened the material must

be injected within 2 hours as otherwise bacterial contamination and growth will occur

"*Selection of cases*—Before giving injection to a patient, it is advisable to examine the urine for albumin and casts but this is not absolutely essential Even where no urine is available or where the patient is in an extreme state of collapse or the urine shows traces of albumin (as most cases of advanced starvation do), peptone glucose may be safely administered But if there is general œdema, and if kidney and liver damage is suspected it will probably be advisable to adopt other methods of treatment

"Nutritional œdema cases may improve markedly after peptone glucose injection

Technique—The intravenous injections are best given with the help of Haye's pattern transfusion set The screw cap of the bottle is removed and the cork of the transfusion set (previously washed and sterilized) fitted on to the bottle. The bottle is inverted and hung up and the clamps on the rubber tubing adjusted till the fluid comes out in drops (60 per minute) from the needle. The latter is then introduced into the vein and the fluid allowed to go in slowly An injection of 200 ccm should take an hour to administer Rapid administration may not be tolerated well 400 ccm is the maximum daily dose It may be given in one dose or preferably in two doses of 200 ccm each, one in the morning and the other in the evening The effect is often immediate and lasts about 24 hours The cases generally need as many as three injections on 3 consecutive days A total of 600 to 1 000 ccm in 3 days often results in marked improvement and should be supplemented by nasal feeding (vide infra) or by hospital diet by mouth as indicated It is essential to remember th [illegible] 100 to 200 calories and, there [illegible] proper diet. So far there has [illegible] 3 days but if required they [illegible]

'*Reactions*.—In none of the cases so far injected has any adverse reaction been noted Improvement in the pulse respiration, blood pressure and general condition usually follows the injection In a few cases a latent malarial infection has flared up after one or more injections and prompt treatment with anti-malarial drugs has cured the disease

"*Cleaning and sterilization*—After using the transfusion set, it should be immediately washed thoroughly in clean water and resterilized for use This is important, as otherwise the fluid in the set may decompose with the formation of toxic substances which if not properly washed may give rise to untoward results

Intravenous administration of peptone glucose solution has been replaced by protein hydrolysate in the treatment of inanition. The following account of its preparation and its use in the treatment of inanition is abstracted from Krishnan et al I M G April 1944. P 160

(2) Protein Hydrolysates in the treatment of Inanition

"*Historical*—Henrique and Anderson (1913) were the first to show that hydrolyzed proteins could be safely given intravenously to protein starved animals, and that they supported life and growth and maintained the animals in nitrogen equilibrium Elman (1942) and Elman and Lischer (1943) found that solutions of amino acids and peptides can be administered intravenously to man in fair amounts without any very serious reactions and that nitrogen equilibrium could be maintained by their use.

"*Methods of preparation known*—Protein hydrolysates have been prepared by one of two ways (1) Acid hydrolysis and (2) Enzyme hydrolysis.

Acid hydrolysis is the easier method but in this method at least one essential amino-acid (tryptophane) is destroyed by the hot acid and has to be separately prepared and added to the hydrolyzed mixture which makes the product expensive Acid hydrolysates are fairly satisfactory though not absolutely safe in all cases.

Enzyme hydrolysis is not difficult and is quick and cheap but in this method the hydrolysis is generally incomplete and the mixture may contain in addition to amino acids and simple peptides, higher polypeptides which produce allergic or other reactions

Amino-acid Mixtures—Mixtures of the ten es . . .
also been tried While somewhat enc . . .
of the opinion that pure amino aci . . .
hydrolysate mixtures. Moreover, th . . .
consuming and expensive.

Choice of ferment and substrate—From a careful study of the methods of preparation described above, Krishnan and co workers (1944) concluded that a properly prepared enzymic hydrolysate would be the cheapest and best product for parenteral therapy Pancreas trypsin has two disadvantages Firstly, the optimum temperature of its action is 37°C, and bacterial contamination is difficult to avoid during digestion Secondly, there is always the risk of the presence of histamine or histamine-producing enzymes in pancreas trypsin.

The vegetable proteolytic enzyme papain which is readily available in large quantities at a low cost is the best. Its optimum temperature of action is 50°C and the products obtained are free from histamine While the hydrolysis produced by papain is not quite so extensive as that produced by trypsin, this does not appear to be a handicap from the immunological and therapeutic points of view Meat proteins were selected for the substrate as its action on casein and vegetable proteins is more limited.

Preparation of hydrolysate.—The protein hydrolysate prepared in the All India Institute of Hygiene is a papain digest of meat (vide Narayanan and Krishnan, 1941) The digestion is conducted at 50°C. for 24 hours The extent of digestion is then tested by determination of formol titre total solids and total nitrogen A fractional analysis of the product is also made The values obtained are used as guides for standardization of the product. The und . . . which are usually small in amount and which are likel . . . removed by repeated heat coagulation at pH7 Bacte . . . gh the use of an aseptic technique and a preservative . . . d with glucose and sodium chloride so as to give a mixture containing 5 per cent protein hydrolysate, 5 per cent glucose and 0 85 per cent sodium chloride. The mixture is then sterilized and tested before issue, biologically on cats for toxicity bacteriologically for sterility, and immunologically for allergic reaction.

Analysis of the mixture has revealed that it contains riboflavine nicotinic acid and thiamin and these are of additional value in increasing the therapeutic efficiency, in promoting glucose utilization particularly in vitamin-starved individuals

(3) Rationale of therapy in inanition

Just as glucose is administered intravenously as a means of supplying predigested . . .

Protein food may be administered by mouth but it will need to be digested and absorbed . . .

Hydrolysate and serum or plasma—Two questions may be asked (1) why not give these hydrolysates orally and (2) why not give serum or plasma intravenously instead of the protein hydrolysate? The answer to the first question is that protein hydrolysates can be given orally but in patients with advanced inanition and collapse absorption is

To the second question the answer is that tissue proteins and serum proteins are not directly interchangeable The latter have to be autolyzed, and the amino-acids made available for synthesis In advanced cases of starvation where there is dehydration the need for tissue proteins is more urgent than the need for serum proteins which may be apparently normal due to the hæmoconcentration. Thus if serum is given its utilization will depend [illegible] esponsible for [illegible] The enzyme [illegible] be attained as [illegible]

indirectly helps in the synthesis of tissue protein from the amino-acids suppl ed. The vitamins present help in the metabolism of glucose

Many thousands of patients were treated with this hydrolysate with excellent results The hydrolysate by the intravenous route is well tolerated and reactions are few and often mild. The only definite contra indication is nephritis. The injections are well tolerated even in presence of pneumonia dysentery and other infectious diseases but specific treat ment for these cond tions should of course be given

The immediate reaction to injections is good the pulse and general condition improve but in severe cases several injections may have to be given In some severe cases no improvement results and the patient dies

Dietetic treatment—The concomitant diseases occurring in these patients are treated on usual lines. Oedema and anæmia disappear by proper diet and drug treatment.

The d et should be l ght and easily d gestible in the beginning consisting mainly of milk, ghol conjee, fruit juice, etc. When he gets stronger gruel diet may be given followed by solid food

2. Nutritional Œdema

This condition is due to long continued subsistence on low diet deficient in proteins generally and of biologically complete proteins particularly This gives rise to changes in the concentration of plasma proteins altered osmotic pressure of the blood and consequently to oedema which may become generalised The condition occurs especially in war and during famine periods hence the name "War œdema" or 'Famine œdema' But considering the number of starvation or semi starvation cases incident to war and famine cases of nutritional œdema have not been very many Patients have been seen emaciated down to skin and bones but without œdema It is possible that some other factor (viz, liver damage) is necessary besides starvation to produce nutritional œdema

The œdema usually develops when the diet is of low caloric value and with protein contents of less than 40 gm daily The total proteins of the plasma are thus markedly reduced and inversion of normal albumin globulin ratio takes place giving rise to retention of water in the tissues Occasionally such œdema occurs even when the total plasma protein level is in the normal range In these cases it is found that the albumin fraction is low and that the globulin frac tions are increased the osmotic pressure of the globulin fraction being much lower than that of the albumin fraction

Clinical aspects—As a result of low diet there is progressive loss of weight though this is made up later by retention of water In the early stages there is pitting œdema of the lower extremities, later this becomes generalized, and if progressive leads to general anasarca Diagnosis is confirmed by the determina tion of total plasma proteins (normal 6 5 to 8 5 gm per 100 ccm) and albumin globulin ratio (normal albumin 4.2 to 5.7 gm, globulin 1 3 to 3 0 gm per 100 ccm)

In the early stages the total plasma protein is unchanged the albumin is somewhat reduced and globulin correspondingly increased Later the total protein is reduced with inversion of the normal albumin globulin ratio Treatment consists in giving high protein diet (100 gm or more daily) with more vitamins *Mercurial diuretics are helpful if the œdema is marked*

3. Epidemic Dropsy

Introductory—Rice eating people are prone to suffer from a condition of œdema which is frequently epidemic and not connected with the usual cardio-renal causes It was pointed out by Megaw that the condition in one extreme presents the syndrome of epidemic dropsy (fever, rash gastro intestinal symptoms capillary dilatation glaucoma, etc) and at the other extreme the picture of chronic beri beri with peripheral neuritis While there may be some resemblance between the two, epidemic dropsy is now considered as a distinct and separate clinical entity

The distinctive features are that *in epidemic dropsy there is no evidence* of peripheral neuritis excepting pains and aches in the muscles especially of the calves Fever is usually present which is seldom present in beri beri Gastro intestinal irritation indigestion and diarrhœa which are very common in epidemic dropsy are not encountered in beri beri The erythematous rash and vascular nodules (sarcoids) are characteristic features of epidemic dropsy Common complications such as glaucoma, abortions hæmorrhages, etc, of epidemic dropsy are not seen in beri beri Sucklings are affected in beri beri but infantile epidemic dropsy is unknown

Historical—In 1876-7 during a great famine in southern India 'beri beri made its appearance its chief symptoms were swelling in the legs palpitation and breathlessness on exertion In 1877 an outbreak occurred in Calcutta after the rains and continued through the cold season it recurred in the winters of 1878 and 1879 and ma nly attacked the Bengalis *A similar epidemic broke out in the island of Mauritius in November 1878* and continued till April 1879 the disease be ng apparently conveyed there by the labour forces from Calcutta Outbreaks occurred in Calcutta in 1901 in 1907 8 and 1909 a special feature being neuritis in some cases Greig who investigated the last outbreak found that mortality was high that it closely resembled ship beri beri and the cause was faulty d etary Epidemics also occurred in 1910 1919 1926 1927 1929 1930 and the largest which occurred in 1934 35 affected not only Bengal but the adjoining areas of Assam Bihar and the United Provinces The disease was prevalent in places where *parbo led rice and mustard oil enter into the dietary* the chief centres being Bengal Assam B har and Orissa and the adjoining portions of the United Provinces Small outbreaks have also been reported from Burma Madras and the Central Provinces the disease in almost all cases was mainly confined to rice eaters

Seasonal and class incidence—Although outbreaks may occur at any t me during the year the main incidence of the disease is during or after the rainy season the epidemic tails off during the cold weather months and then disappears altogether by April Males and females are equally affected In Calcutta the Marwaris and Europeans usually escape because they consume l ttle or no rice and do not use mustard oil for cooking The disease is prevalent amongst the upper and middle classes the poorer labouring classes often escaping These people often cannot afford mustard oil for cooking and also they do not throw away the rice water

(1) Aetiology

Food deficiency theory—Epidemic dropsy was once believed to be a nutritional disorder similar to beri beri That it is different from beri beri is shown by its prevalence in families in whom there cannot be any question of a diet deficient in vitamins It never occurs in infants whereas infantile beri beri is well known The characteristic cutaneous manifestations of epidemic dropsy glaucoma and abortion are not seen in beri beri Vitamin therapy is effective in beri beri but not in epidemic dropsy

Rice toxin theory—In many epidemics studied rice was incriminated as the causative agent and the rice toxin theory was formulated It was suggested that the starch cells of rice especially that which after parboiling and milling is stored in damp, ill-ventilated places become infected with a Gram positive proteolytic bacterial organism. A histamine-like water soluble toxin is said to be produced as a result, and it is claimed that spores [illegible] organisms are characteristi [illegible] infected rice grains often [illegible] be spotted by putting the [illegible] sed grains can at once be [illegible] During an epidemic stop [illegible]

[illegible] The disease is almost confined [illegible] t, and relapses are [illegible] to be proportionate [illegible] locality has started [illegible] st the rice theory — (1) Rice collected from unaffected families in an extensive epidemic in Manbhum District, [illegible] isolated from infected rice are not pathogenic to laboratory animals

Mustard oil theory—Mustard oil has been suspected repeatedly for the last half century This was incriminated mainly because Marwaris and Europeans who do not use [illegible] and on animals (Chopra et al, 1939) with very suggestive results It has been shown that argemone oil a common adulterant of mustard oil can produce symptoms of epidemic dropsy even in small quantities Lal and his associates (1941) place the maximum safe amount at 0 5 per cent

Infection theory—A specific bacterial or virus infection has been suggested from time to time but there is no direct positive evidence in support of this view although the seasonal prevalence, endemicity, uniform pathological changes and clinical features and epidemics outbreaks all point to an infection.

(2) Pathology

[illegible] fic action on smaller blood vessels in the skin [illegible] dilatation of the papillary and sub-papillary [illegible] capilliary permeability and œdema. Prolifera- [illegible] them with endothelial cells produce vascular [illegible]

The lesions are from pin point to an inch or more in diameter and are not of inflammatory nature. There is often increased pigmentation of the basal layer The heart is enlarged, the right side more than the left, the individual muscle fibres are widely separated from each other by engorged capillaries and transudative œdema, and cardiac inefficiency results. The lungs may be congested and œdematous, hydrothorax is often present, the liver spleen, intestines etc., generally show dilated vessels and congestion. In the eyes, the uvea is engorged with over production of aqueous humour which may cause glaucoma

(3) Symptomatology

The onset may be sudden or insidious. Premonitary diarrhoea is common, there may be a sudden attack of diarrhœa with or without nausea and vomiting The patient usually

In the early stages the total plasma protein is unchanged the albumin is some what reduced and globulin correspondingly increased Later the total protein is reduced with inversion of the normal albumin globulin ratio Treatment consists in giving high protein diet (100 gm or more daily) with more vitamins Mercurial diuretics are helpful if the œdema is marked

3. Epidemic Dropsy

Introductory—Rice eating people are prone to suffer from a condition of œdema which is frequently epidemic and not connected with the usual cardio renal causes It was pointed out by Megaw that the condition in one extreme presents the syndrome of epidemic dropsy (fever rash gastro intestinal symptoms, capillary dilatation glaucoma etc) and at the other extreme the picture of chronic beri beri with peripheral neuritis While there may be some resemblance between the two epidemic dropsy is now considered as a distinct and separate clinical entity

The distinctive features are that in epidemic dropsy there is no evidence of peripheral neuritis excepting pains and aches in the muscles especially of the calves Fever is usually present which is seldom present in beri beri Gastro intestinal irritation indigestion and diarrhœa which are very common in epidemic dropsy are not encountered in beri beri The erythematous rash and vascular nodules (sarcoids) are characteristic features of epidemic dropsy Common complications such as glaucoma, abortions hæmorrhages etc of epidemic dropsy are not seen in beri beri Sucklings are affected in beri beri but infantile epidemic dropsy is unknown

Historical—In 1876-7 during a great famine in southern India 'beri beri' made its appearance its chief symptoms were swelling in the legs palpitation and breathlessness on exertion In 1877 an outbreak occurred in Calcutta after the rains and continued through the cold season, it recurred in the winters of 1878 and 1879 and mainly attacked the Bengalis A similar epidemic broke out in the island of Mauritius in November 1878 and continued till April 1879 the disease being apparently conveyed there by the labour forces from Calcutta Outbreaks occurred in Calcutta in 1901 in 1907 8, and 1909 a special feature being neuritis in some cases Greig who investigated the last outbreak found that mortality was high that it closely resembled sh p beri beri and the cause was faulty dietary Epidemics also occurred in 1910 1919 1926 1927 1929, 1930 and the largest which occurred in 1934 35 affected not only Bengal but the adjoining areas of Assam Bihar and the United Provinces The disease was prevalent in places where parbo led rice and mustard o l enter into the dietary the chief centres being Bengal Assam Bihar and Orissa and the adjoining portions of the United Provinces Small outbreaks have also been reported from Burma Madras and the Central Provinces the disease in almost all cases was mainly confined to rice eaters

Seasonal and class incidence—Although outbreaks may occur at any time during the year the main incidence of the disease is during or after the rainy season the epidemic ta ls off during the cold weather months and then disappears altogether by April Males and females are equally affected In Calcutta the Marwaris and Europeans usually escape because they consume little or no rice and do not use mustard oil for cooking The disease is prevalent amongst the upper and middle classes the poorer labouring classes often escaping These people often cannot afford mustard oil for cooking and also they do not throw away the rice water

(1) Aetiology

Food deficiency theory—Epidemic dropsy was once believed to be a nutritional disorder similar to beri beri That it is different from beri beri is shown by its prevalence in families in whom there cannot be any question of a d et deficient in vitamins It never occurs in infants whereas infantile beri beri is well known The characteristic cutaneous manifestations of epidemic dropsy glaucoma and abortion are not seen in beri beri Vitamin therapy is effective in beri beri but not in epidemic dropsy

Rice toxin theory—In many epidemics studied rice was incriminated as the causative agent and the rice toxin theory was formulated It was suggested that the starch cells of rice, especially that which after parboiling and milling is stored in damp, ill ventilated places become infected with a Gram positive proteolytic bacterial organism A histamine-like water soluble toxin is said to be produced as a result and it is claimed that spores of the bacil … rganisms are characteristi cally predor … infected rice grains often show a cen … be spotted by putting the rice in a pe … sed grains can at once be seen and if … During an epidemic stop rice and tal

The points in favour of the rice hypothesis are —(1) The disease is almost confined to rice-eaters (2) Rapid improvement follows stopping of rice diet and relapses are common when it is resumed (3) The severity of the disease is held to be proportionate …

… isolated from infected rice are not pathogenic to laboratory animals

Mustard oil theory—Mustard oil has been suspected repeatedly for the last half century This was incriminated mainly because Marwaris and Europeans who do not use …

… f Tropical Medicine on human volunteers … suggestive results It has been shown that … oil can produce symptoms of epidemic … ssociates (1941) place the maximum safe amount at 0·5 per cent

Infection theory—A specific bacterial or virus infection has been suggested from time to time but there is no direct positive evidence in support of this view although the seasonal prevalence, endemicity uniform pathological changes and clinical features and epidemics outbreaks all point to an infection

(2) Pathology

The 'toxin' appears to have direct specific action on smaller blood vessels in the skin heart, muscle and other tissues Marked dilatation of the papillary and sub papillary blood vessels of the skin leads to increased capillary permeability and œdema. Proliferation of small vessels and infiltration round them with endothelial cells produce vascular growth commonly called "Sarcoids"

The lesions are from pin point to an … nature There is often incre … the right side more than the … each other by engorged capil … The lungs may be congested … intestines etc, generally sho … engorged with over productio …

(3) Symptomatology

The onset may be sudden or insidious Premonitary diarrhoea is common, there may be a sudden attack of diarrhoea with or without nausea and vomiting The patient usually

ascribes this to some error in diet but is surprised to find swelling in the legs when the condition is actually recognized. Initial œdema is of the solid type and the skin over it may be tense, flushed shiny and warm The œdema does not usually extend above the knees but may in some cases affect the thighs sacral region body and upper extremities Hyperpigmentation may occur in the skin of the hands feet and face 'Sarcoids' occur in some cases and may appear even on mucous surfaces of the mouth and nose They vary in size from a pins head to a walnut and begin as tiny red papules which gradually increase in size, after a varying period they dry up and disappear, leaving a pigmented area Large 'Sarcoids' are prone to become pedunculated and infected with pyogenic organisms Hæmorrhage is apt to occur (Chopra and Chaudhari 1935)

Clinical aspects—Fever of a mild remittent or intermittent type especially in the acute stage is common Dyspnœa an early feature, is complained of before gross evidence of the cardiac damage appears Anæmia may be present The blood pressure is variable and the pulse rate is usually rapid and may be irregular The condition of the heart can be classified into three groups (*a*) *Acute or fulminating* in which the patient has the heart affected from the very start failure progresses and death may occur within four to seven days These cases resemble the picture of an acute left heart failure This type with a high mortality was common in the epidemics of 1926 and 1927 (*b*) *Subacute or Chronic* here the heart is less rapidly affected and failure from which recovery is usual is a slow process These cases resemble the picture of a combined right and left sided failure with slight cyanosis jugular distension and general systemic venous congestion This occurred in the 1932 epidemic (c) *Formes frustes* here the heart either wholly escapes or is very slightly affect[illegible] The
existence of these three distinct types [illegible]
of histological changes in the heart wa[illegible]
of these three modes of cardiac fail[illegible]
dilatation The degree and severity o[illegible]
weakness are directly proportionate to the degree and extent of capillary dilatation that [illegible]

syncope and death may result

While cardiac involvement is the rule its severity is not uniform In certain epidemics, severe diarrhœa is the predominant symptom and the cardiovascular symptoms are of a mild nature In patients with constipation the cardiac features usually progress rapidly and become serious often leading to a fatal end In yet another group mild cardiovascular symptoms are associated with a high rate of ocular complications such as glaucoma, there is as a rule only slight diarrhœa and œdema of the legs in these patients Diarrhœa is probably produced by the toxic bases in the intestines which not only damage the capillaries and produce œdema but also produce exfoliation of the mucous lining of the gut

The liver is often enlarged and tender Ascites may occur in severe cases. Cough dyspnoea and orthopnoea are observed in some cases and are due to the cardiac condition œdema of lungs or pleural effusion Rectal congestion may cause painful piles

Neuritis is rare and the knee jerks though they may be diminished are seldom lost There is no impairment of sensation or motor power General asthenia, loss of appetite weakness and insomnia are common Glaucoma of a primary non inflammatory type is common, haloes are seen around lights followed by a progressive dimness of vision tension rises high and the field of vision is gradually contracted leading to complete blindness

Abortions are common in pregnant patients The blood picture usually shows anæmia, generally of the macrocytic ortho-chromic type

Course—The disease may run an acute or a chronic course In acute cases cardiac failure which is present from the onset rapidly progresses and death may follow in a few days The sub-acute or chronic cases recover in a few weeks or may hang fire for months (asthenic type) the duration averaging about six weeks The patient is usually incapacitated for regular work for a long time Palpitation breathlessness on exertion precordial pain and general weakness usually persist for a long time The patient may lose his sight if the symptoms of glaucoma are overlooked

Prognosis—Prognosis depends on the severity of the disease and complications, and as a rule is favourable The average mortality is between 2 and 8 per cent.

(4) Prophylaxis and Treatment

According to our present state of knowledge prophylaxis should aim at avoidance of mustard oil contaminated with argemone oil for which proper public health measures should be adopted Admixture of mustard seeds with argemone seeds during harvesting is to be guarded and every sample of oil tested for presence of argemone oil before consumption. Simple tests —(1) Nitric acid (2) Cupric acid (3) Ferric chloride

(5) Treatment

During an epidemic, exclusion of rice and mustard oil from the diet is advisable if possible, or else prohibition of parboiled rice and use of pure mustard oil are recommended A careful watch should be kept over the cook and servants during an outbreak Affected cases should be as far as possible isolated

All acute cases should be strictly confined to bed until convalescence is well advanced The intestines should be cleared by an initial purgation and fluids should be given freely to eliminate the toxins It is not advisable to check diarrhœa especially in the initial stages If it is very severe and exhausting kaolin or bismuth preparations may be prescribed Intestinal antiseptics are advocated but are useless

Rice should be completely eliminated from the diet and bread or chappatis given instead If possible the patient should be removed from the endemic area It is advisable to exclude mustard oil from the diet altogether, but if this is impossible pure mustard oil obtained from jails should be used If there are some gastro-intestinal symptoms milk or its preparations such as lime-whey and butter milk with fruit juice and glucose should be given at first and then other articles may be added gradually as the condition improves Otherwise the diet should be well balanced as far as possible

Thiamine hydrochloride (Vit. B_1) in large doses should be given in severe cases, in view of the great success of this drug in the similar condition of heart-failure in beri beri

For the cardio capillary crises complete rest in bed, adrenaline in doses f 3 to 5 minims of a 1 in 1 000 solution or ephedrine (action more lasting) ntramuscularly or preferably a tincture of ephedra vulgaris 20 to 30 minims to 3 times a day may be given Ephedra vulgaris contains both ephedrine d pseudo-ephedrine the latter alkaloid being particularly abundant in the dian variety Ephedrine acts on the vasomotor nerve endings and its action much more sustained than that of adrenaline Pseudo ephedrine has a weak so motor stimulant action but is direct stimulant to the myocardium The mbined action of the two alkaloids is responsible for the effectiveness of s drug in epidemic dropsy It is advantageous to give 10 grains of calcium ate with each dose If much œdema is present theobromine and sodium cylate (diuretin) may be prescribed in 10 grain-doses with the tincture of edra with or without mercurial diuretics

Drugs of the digitalis group strophanthin and euphyllin are of little value reating the cardiac symptoms Glucose and stimulants such as cardiazol min or injection of camphor in oil have more effect in such cases Blood g is helpful in congestive cases and as much as 500 ccm or more may be ved Injections of atropine sulphate dry cupping and inhalation of oxygen to combat œdema of the lungs Ascites or hydrothorax may require entesis

Small bleeding sarcoids can be successfully dealt with by carbon dioxide *snow*, and large pedunculated ones are preferably removed under local anaesthesia

For the treatment of glaucoma as *long as the visual fields do not show* any change there is no need for immediate operation but as soon as defects in the visual fields become evident operation must not be delayed

Convalescence—Patients should be given general tonics to combat the anæmia and general asthenia and to expedite convalescence Heavy exercise *should be avoided for a long time and the eyes should be* periodically examined Rice should be restored into the diet very gradually and with caution

4. Beri-Beri

The term beri beri is applied to a syndrome characterised by multiple peripheral neuritis and in severe cases by congestive cardiac failure, *which occurs* mainly in tropical and subtropical climates either endemically or in form of epidemics It is a deficiency disease due to lack of vitamin B (thiamine), and *other vitamins also*

Historical and general—Beri beri was known in China many centuries ago In Japan the disease has long been known under the name of Kakke meaning weakness of the legs The name beri beri is probably derived from a Malayan word *biribi* meaning a jerky gait Malcolmson (1835) pointed out that both the dropsical and paralytic manifestations often occured in the same individual in India and that they might appear simultaneously or might succeed one another The neuritis of beri beri has been shown to be of the same type as alcoholic aresnical or diphtheritic neuritis

Beri beri was largely spread in the past in oriental countries where polished rice was a staple article of diet It is thus seen in the tropical and sub-tropical climates of the Eastern hemisphers the largest number of cases having being reported from China In India it is encountered mostly in the north east coastal area. It has been prevalent even *in cold countries such as Labrador Newfoundland Iceland etc among people living mainly* on white flour

Beri beri occurs more commonly in men and among women during pregnancy and *lactation being less common in children It may occur in the breast fed infants of mothers* with beri beri and infantile beri beri has a high mortality rate Most of the cases occur during or after the hot or damp season the disease disappearing shortly after the new rice crop has come in

(1) Aetiology

There are a number of theories regarding the causation of beri beri (1) toxic theory, [illegible] nfect on theory (3) diet deficiency theory and (4) combined toxic and deficiency [illegible] is a deficiency [illegible] of the vitamin [illegible] *ation thyrotoxi* [illegible] hronic digestive disorders to faulty storage and utilization as [illegible] nterference with *normal* biosynthesis of the vitamin in the gut Some hold that deficiency of vitamin B_1 is not the whole story of the ætiology of beri beri ard probably there is some other factor For instance the combined toxic and deficiency theory assumes that in some samples of rice and occasionally also in other articles of diet there is a poison which causes a multiple neuritis and that vitamin B is an antidote to this poison *The interaction of dietetic* poisons and the antidotal action of vitamin B would satisfactorily account for all the puzzling variations in the symtoms of beri beri Serious defect in vitamins might result *in the small doses of* poison present in many samples of rice producing chronic neuritic forms of the disease corresponding to the experimental polyneuritis of birds which have been fed on polished rice On the other hand in cases in which the poisons were present in large amounts the normal amounts of vitamin B_1 would be insufficient to prevent them from causing grave and acute symptoms Between these extremes would come all the many intermediate forms of the disease caused by various combinations of the doses of the poison and the antidote The dramatic curative effect of massive doses of thiamine [illegible] *severe cases in which the patient is overwhelmed by the poisons* would be fully explained

(2) Pathology

The heart and the nervous system are affected The cardiac changes are hypertrophy and dilatation the striking microscopic feature being intercellular œdema. Fragmentation, fatty and hydroscopic degeneration of the cells may be found Degenerative lesions with
[illegible] -erves of the legs are usually
[illegible] he lesions may occur in the
[illegible] and posterior nerve roots),
[illegible] the phrenics are frequently
[illegible] he disease With the distur bance in nerve supply there is secondary atrophy of muscles Marked disturbance of the mechanism which controls water balance in the tissues, occurs in some acute cases

(3) Symptomatology

The symptoms of the disease are referrable to (i) lesion of the nervous system, (ii) cardiac changes, and (iii) secondary effects of œdema.

The disease has two distinguishable stages —

(1) A period of alimentary disturbances during which there is a feeling of heaviness in the epigastrium sometimes accompanied by nausea and vomiting, and (2) a period of polyneuritis during which there is palpitation, shortness of breath cyanosis and weakness Dry beri beri, wet beri beri and atypical beri-beri have been described which, however are not distinct but merge into each other The prominent clinical types distinguished are described below —

The chronic dry type—This type starts insidiously with slight gastro-intestinal disturbances, wasting and weakness of muscles, especially the ones mostly used, viz extensor muscles of the thighs The knee jerks are often exaggerated at first but are later lost Tachycardia is present early and palpitations and shortness of breath are usual The course of the disease is chronic, and at any time swelling may occur so that the case presents a picture of dropsical or wet beri beri

Peripheral neuritis—All or some of the symptoms due to the peripheral neuritis *e g*, muscle tenderness muscular wasting and weakness, nerve tenderness and varying degrees of impairment of sensation paræsthesiae are present Deep sensibility of the Achilles tendon is lost. Ataxia, finally flaccid paralysis, foot drop and wrist drop may develop In some cases cloudiness of vision or photophobia may occur

In severe cases cardiac failure occurs, affecting chiefly the right auricle and ventricle Præcordial pain is common

In mild cases the disease lasts for a few weeks and subsides gradually In severe and prolonged attacks, convalescence is slow and the patient remains weak for months or even years The course of a case depends very much on the treatment given With early diagnosis and prompt treatment, the disease can be arrested within a few days, but if allowed to progress unchecked the nerves become seriously damaged and restoration of function is slow and may never be complete

Wet beri-beri—In this form there is a gradual onset of œdema which may be generalised with breathlesness on exertion Signs of neuropathy are often not prominent and the œdema masks the muscular atrophy There may be enlargement of the heart, marked jugular pulsation and systolic murmur The blood pressure falls an injection of adrenaline further lowers the diastolic pressure The electro-cardiogram shows right axis deviation, alteration of T waves and prolongation of Q-T. interval

Acute cardiac type—The attack may begin with cardiac symptoms but usually the heart fails after the disease has been present in a mild or moderate form for several weeks. In this type of the disease intoxication predominates, though vitamin deficiency also plays a part [illegible]
onset of [illegible]
feeble p[illegible]
and hyd[illegible]
within a few days

Atypical beri beri—This is beri beri modified by other nutritive disorders such as pellagra, scurvy or ship beri beri or nutritional oedema Sub-clinical beri beri is also not uncommon and presents symptoms such as weakness, anæmia, vague pains, mental depression and tachycardia resulting in a syndrome resembling neurasthenia

Infantile Beri beri—Infantile beri beri first described by Hirota (1898) is encountered mainly in the Philippines and Japan *but isolated cases probably occur wherever beri beri* is prevalent The disease occurs in breast fed infants whose mothers are suffering from frank or latent beri beri (toxin in mother's milk suggested as cause) The first warning is that urinary secretion is diminished. Fretfulness anorexia low fever wasting pallor vomiting and diarrhœa or constipation are usual The child cries constantly and meningismus aphonia and convulsions may occur Oedema and cardiac hypertrophy are nearly always in evidence, and sudden attacks of dyspnœa, which are often fatal may occur Pathological changes are identical with those occurring in wet beri beri

In the treatment of such cases the infants should be taken off the *mothers breast*, and fed by a healthy wet nurse or on a suitable artificial diet rich in all the vitamins. Injections of vitamin B_1 should be given and these have been reported to give excellent results Extract of rice polish has given good results

The mothers should be properly fed during pregnancy and lactation When a mother's diet is deficient, rice polish extract should be given to the child daily till six months old

Prognosis—Mortality may be as high as 60 to 70 per cent, but even without treatment usually below 30 per cent The chronic type may leave muscle weakness or flaccid paralysis due to degeneration of nerve cells Recovery in adults is slow and muscle weakness and neuritis may persist for months With early and adequate treatment the disease can usually be arrested within a few days especially in the infantile type

One attack predisposes to others, and persons who have once suffered should be advised to avoid a rice diet for prolonged periods

(4) Treatment

The two principal requirements in the treatment of beri beri which must always be kept in mind are the prohibition of rice and any other food such as edible oil which is likely to be toxic and the provision of a diet rich in *proteins and all the vitamins Meat, eggs milk and leafy vegetables are given* freely Fresh milk and orange juice are given when gastro intestinal symptoms are present

Vitamin B_1 (thiamine chloride) should be given in doses *of 10 to 20 mgm* parenterally once or twice daily In the presence of cardiac failure intramuscular and intravenous injections of 20 to 50 mgm are advised daily till the heart and circulation become normal, often this may result in dramatic improvement [illegible] the cheaper concentrated extracts [illegible] most cases Excellent results [illegible]istration of *tikitiki*, (alcoholic [illegible]nces daily Brewers yeast in [illegible] be given

In cases of cardiac dilatation all appropriate measures for management of *acute congestive failure should be adopted* Complete rest in bed should be enforced and blood *letting may prove a life saving measure Distention of the* veins of the neck and cardiac distress are the indications for this measure Extensive plural effusions should be relieved by tapping Mercurial diuretics may have to be resorted to for increased diuresis

Alcohol and arsenic are especially harmful and should be avoided

In chronic type of disease, besides rest and nourishing diet massage and passive movements should be carried out Postural treatment with or without splints may be necessary to prevent deformities

Unaffected members of families or institutions in which outbreaks have occurred should be dealt with in the same manner as those who have been attacked

Prophylactic measures—The general principles of treatment apply equally to prophylaxis. Under milled rice should be used and rice should be stored in a dry, cool and well ventilated storehouse. The period of storage should be as short as possible. Stocks of rice suspected of causing beri beri should not e used for human consumption. Wetted rice should be thoroughly dried as oon as possible before storage. Edible oils used for cooking should be regarded s possible sources of intoxication.

The diets should be wholesome and rich in vitamins. Eggs, meat and getable should form part of the diet, unfortunately beri beri is a disease of poverty. Rice diets should be supplemented by articles of diet which are more nutritious. Soya beans and other leguminous seeds are considered to have a great protective value against beri beri.

Test for under milled rice—Place rice in a small dish and cover it with Gram's iodine solution. The exposed starch turns black with iodine. If the rice is completely decorticated the entire grain turns black; if it is undermilled it is only partly stained.

In chemical test the index proposed is 1.77 per cent phosphorous pentoxide, plus fat or any rice not having less than 0.62 per cent phosphorous pentoxide. Such rice does not produce polyneuritis in pigeons.

5. Pellagra (also known as Psilosis Pigmentosa, Alpine Scurvy)

Pellagra (rough skin) is an endemic disease characterised by dermatitis nd pigmentation of the skin especially of the exposed parts, gastro-intestinal isturbances and often certain mental symptoms which may be followed by ue psychosis. It was first described by Casal (1725) and was known to the aniards as 'mal de rosa'.

Geographical distribution—Pellagra is largely confined to maize eaters being particularly prevalent in the Balkan States, Turkey, Greece, Spain, Portugal, Lower Egypt, Mexico, Brazil, Argentina, Jamaica and the Southern States of the U.S.A. Sporadic cases occur in India and the disease is frequently seen in maize eating areas in the Kashmir valley. Pellagra attacks chiefly the poorer labouring classes especially in warm climates. It has a definite seasonal incidence occurring predominantly in the winter of warm countries and in the spring and early summer of the temperate zones.

(1) Aetiology

Goldberger (1914) considered it a deficiency disease and he produced a condition known as 'black tongue' in dogs (which is analogous to pellagra in man) by feeding them on a pellagra producing diet. Black tongue could be cured by yeast and subsequently pellagra in man was also found to be cured by its use. The factor responsible for cure in the yeast was termed by him as the P.P. factor. Elvehjem (1937) found that the factor in yeast responsible for cure of black tongue was nicotinic acid. Later cases of human pellagra were successfully treated with nicotinic acid (niacin) or nicotinic acid amide (niacin amide). All the symptoms even the mental symptoms disappeared whether it vas given by mouth or parenterally. Such cured cases, however developed symptoms of iboflavin deficiency or thiamin deficiency or both which could be treated by administration of these substances. Vitamin B_6 and pantothenic acid also controlled other symptoms ellagra is thus a deficiency disease due chiefly to lack of nicotinic acid (niacin) but some extent to deficiency of other fractions of vitamin B complex. Such articles as lk, meat, eggs etc., which are protective are rich in nicotinic acid.

Other theories regarding the causation of pellagra are as follows —

The maize intoxication theory—The distribution of the disease corresponds closely h that of maize, and there is evidence that maize which has been damaged during age is especially liable to cause the disease. Explosive out breaks often occur. The rrence of the skin lesions on exposed parts of the body in pellagra led to the idea maize might contain a photo sensitizing substance analogous to that contained wheat

Chick (1933) advanced a view which is perhaps a combination of several factors She postulated that pellagra may be caused by a toxic substance derived from the maize diet which can be corrected by sufficient quantity of protein or perhaps by sufficient vitamin B which is present in these proteins

Amino acid deficiency theory—The association of pellagra with maize consumption has given considerable support to the theory that the disease might be caused by lack of proteins of high biological value It is suggested that in pellagra certain amino acids were deficient in the diet consumed by the patients The protein of maize flour zein for instance is deficient in certain amino acids such as tryptophane and lysine

Infection theory—No satisfactory evidence has been adduced to show that pellagra can in any way be considered to be directly an infectious disease

(2) Pathology

Dermatitis may or may not be present The skin first becomes erythematous and this is followed by exfoliative dermatitis atrophic changes and pigmentation of the affected area There is marked stomatitis and glossitis at first and later the mucous membrane of the small and large intestine becomes inflammed and ulcerated right down to the rectum The skeletal muscles are wasted and degenerated as is also the cardiac musculature There is degeneration of the neurons of the whole of the nervous system and this is especially *marked in the tracts of Gall and Burdach of the spinal cord The direct pyramidal tract* ... h ch nerve fibres have disappeared. ... of anterior and posterior horns ... cerebral atrophy and increaseed ... treatment

Symptomatology—The disease has a wide range of severity varying from the mild and clinically almost unrecognisable cases to the severe and rapidly fatal types The general course of pellagra is chronic with well marked exacerbations and remissions In general gastro intestinal changes occur during the early stages of the disease and are followed later by symptoms due to degenerative changes in the central nervous system.

In areas where pellagra is prevalent many persons exhibit symptoms of poor appetite indigestion low intelligence soreness of the lips and tongue and general debility These are undoubtedly cases of mild subcl nical pellagra (prepellagra), and a number of such people develop symptoms of frank pellagra at a later stage

Mild type—After a few weeks or months of the above described mild symptoms some of the affected persons become gradually worse The tongue assumes a red and glazed appearance the mouth becomes sore and patches resembling sunburn appear on the dorsum of the hands along the radial border also some time on the back of the arms neck cheeks or nose.

Alternate ... *Scalding sensation in the mouth* (may extend ... loss of appetite and achlorhy dria are pres ... the symptoms become intense, dermatitis app ... number of cases skin eruption may not appe... ases eruption appeared 3 to 5 months after deficient diet Patients however improve but relapse in the spring

Severe type—In severe cases diarrhoea becomes intractable, emaciation is marked dermatitis more pronounced and extensive and definite mental changes are observed Dermatitis when it appears is characterised by being symmetrically distributed In most

...

erythema ... the skin becomes roughened thickened and pigmented and is sharply demarcated from the normal sk n Desquamation occurs later beginning from about the centre of a patch Sore mouth and scarlet glossitis are usually present It has been shown that exposure to sun shine of persons subsisting on pellagra producing diet produces erythema When pellagrins have been treated with niacin sun shine produces no such effect

The nervous symptoms are vague resembling neurasthenia at first but may develop into psychosis in long standing cases *Insomnia is frequent, there is marked depression* which may indicate insanity and may end in dementia Sensory disturbances may take

place Burning of the feet appears before eruptions appear (symptoms of thiamine deficiency) There may be evidence of organic nervous lesion, viz, peripheral neuritis (producing pain in limbs formication, and subacute degeneration of the spinal cord producing increased knee jerks, abnormal gait

The blood is normal in mild cases but in severe cases macrocytic and hypochromic anæmia is present, pernicious anæmia may rarely occur Usual red cell count is 3 to 3 5 millions with 50 to 70 per cent hæmoglobin leucopoenia is always present

Complications—In a long standing and debilitating disease such as pellagra there is always possibility of association with other diseases Dysentery, amœbic or bacillary, may become implanted on a diseased mucous membrane, hookworm tuberculosis or syphilis may occur in pellagra and pernicious type of anæmia is not uncommon Field of vision may be contracted and visual acuity decreased

(3) Diagnosis

Though in established cases when eruptions have developed there is no difficulty in early cases diagnosis is not easy It may be mistaken for sprue but here the characteristic stool and tendency to macrocytic type of anæmia in the latter disease differentiate it Dermatitis venanata and chronic eczema may be mistaken for skin eruptions but sharply defined edges manner of their development and tendency to recurrence every year are helpful diagnostic features A test for ether soluble pigments in urine may solve the difficulty The test is performed as follows —To 10 ccm of urine in a separating funnel 0 2 ccm of glacial acetic acid is added (to make pH 4) 15 to 20 ccm of ether are then added the whole is well shaken and allowed to stand After separation the lower aqueous layer is drained off and the ether is washed with 10 ccm of distilled water To the washed ether extract add 3 ccm of 25 per cent HCl the mixture is shaken in a test tube In positive cases a pink or purple colour develops when HCl is added

(4) Prophylaxis and Treatment

Public health measures in connection with a well balanced diet are essential The preventive action of nicotinic acid and riboflavin has not been worked out

Even comparatively mild cases of pellagra should be prescribed adequate rest in addition to an improved diet Severe cases require complete rest in bed and adequate nursing Skin lesions require to be protected from sunlight and special care should be devoted to the prevention of bed sores and contractures

Diet—The diet should be rich in proteins vitamins and with a high caloric value (3 000 to 4 000 calories) Fresh milk, fresh green vegetables, fruits and fruit juices, eggs, liver, kidney and lean meats are particularly rich in all the constituents of the vitamin B complex and should be advised according to availability and the scruples of the patient Crude liver extracts by mouth, and brewers yeast have been widely used as sources of vitamins in pellagra and help to relieve most of the symptoms, 75 to 100 gm of powdered yeast should be taken daily, mixed either with milk, tomato juice or warm water and salt

Drugs—Nicotinic acid or nicotinic acid amide is best administered orally either in tablet form or in capsules, in doses of 50 to 100 mgm several times a day according to the severity of the case About 500 mgm daily are usually given but in severe cases doses of 1,000 mgm daily have been advised, up to 2,000 mgm daily in divided doses, have been used without undesirable effects

Nicotin [illegible]
are r [illegible]
Afte [illegible]
In P [illegible]
rises to 0 55 mgm per cent Nicotinic acid amide is a normal body constituent and its use is less likely to lead to unpleasant effects such as vasodilatation, diarrhœa, cerebral or cardiac symptoms A single dose of 200 mgm

intravenously may produce dramatic effects Disoriented patients with rambling speech who are unable to swallow become rational in 2 or 3 days

In cases with reduced visual acuity and concentric constriction of fields of vision, response is rapid vision returning to normal in a week. Such doses may produce vasodilatation of the face and upper half of the trunk, itching and burning sensation of the skin diarrhoea, vomiting, or abdominal cramps The drug should, therefore, be administered in small and frequent divided doses, such as 50 mgm every hour, or 100 mgm every two hours

diet of pellagrins besides produc ery frequently also produces other Thus nutritional cardiopathy and peripheral neuropathy do not respond to nicotinic acid therapy, and require treatment with thiamine chloride Angular stomatitis and cheilitis which are sometime present, respond to treatment with riboflavin in doses of about 5 to 10 mgm daily by mouth The severe cases of dermatitis which do not respond to nicotinic acid alone, may also yield to riboflavin therapy

A mixture containing 25 per cent brewers yeast in 67 per cent peanut butter and 8 per cent peanut oil provides a cheap and palatable food that has been found to prevent pellagra and riboflavin deficiencies when given as a supplement for even comparatively poor diets Two ounces of this preparation should be taken daily

The most striking effects of treatment are observed in the improvement effected in the tongue and mouth symptoms The effect is also observed in the psychology of the patient and in the processes of digestion and assimilation, mental symptoms rapidly improve with nicotinic acid in maximum doses and coramine

Pyrazine carboxylic acid compounds and quinolinic acid have therapeutic action resembling nicotinic acid on the mouth and tongue symptoms

achlorhydria after meals A sooth- *ms If there is evidence of neuritis*

(5) Prognosis

Before nicotinic acid treatment was introduced the death rate was high (30 to 60 per cent) With the present treatment, if instituted early, there should be little or no mortality but taking all sorts of cases it does not exceed 2 or 3 per cent It is essential that after treatment the patient should be put on proper dietary otherwise there is bound to be recurrence The cases seen by the author in Kashmir are generally of a mild type

6. Rickets

Rickets is a deficiency disease occurring in infants from a disordered calcium and phosphorus metabolism caused by an insufficiency of vitamin D in the diet or to lack of exposure to sunlight It is characteristically seen during the rapid growth period in infancy *It responds readily to treatment* either with adequate amounts of vitamin D or to exposure to ultraviolet rays provided of course that the diet is not grossly deficient in calcium and phosphorus

(1) *Aetiology*

Vitamin D can be synthesized from ergosterol by the skin tissues by photosynthesis nder the nfl ence of ultraviolet rays with (wave lengths of 2600 to 3150 angstrom

units) It probably acts by helping the absorption of calcium and phosphorus from the [illegible] bone Inorganic serum phosphorus [illegible] of blood is reduced below 3 mgm [illegible] sease the failure of fat absorption [illegible] vitamin D, but also to excessive [illegible] atty acids in the stools A special [illegible] manifests itself

Rickets is essentially a disease of northern climates and is comparatively *rarely* met with in tropical climates, because of the abundance of sunshine Its prevalence in India however, is often under-estimated because though sunshine is plentiful, the diets are often very poor and minor degrees do occur amongst the children

Osteomalacia, or adult rickets is also a calcium phosphorous deficiency disease accompanied by deficient calcification of all bony tissues It is however, fairly commonly met with in the tropics and is endemic in parts of northern India China and Japan In Kashmir, the disease is specially prevalent, on account of the lack of sunshine during the winter months combined with particularly poor diets The disease is seen essentially in women of the child bearing age during pregnancy and lactation, and tends to increase in severity with each successive pregnancy Women who are kept in *purdah* are particularly prone to be affected. Lack of calcium and phosphorous and of vitamin D, in poor dietaries aggravated by the excessive mineral demands on the body during pregnancy and lactation, are the main factors responsible

(2) Pathology

The characteristic changes in rickets are osteoporosis and consequent softening of bones which become flexible This results in craniotabes, deformities of the limbs, spine and thorax There is also defective ossification of the epiphysial cartilages and this results in the epiphysial enlargements of long bones and the beading of the ribs Microscopically, the epiphysial cartilages are very irregular and the normal zones between cartilage and bone are not clearly demarcated The bone cortex is thin and trabeculae are greatly reduced in number or may be absent The shafts of the long bones and also the frontal and parietal bones of the skull s[illegible] tion of soft spongy bone be[illegible] characteristic bossing of bones [illegible] the osteoclasts occur in normal [illegible]

The parathyroid glands are frequently enlarged, probably due to an increased output of parathormone in an effort to maintain the falling serum calcium level by mobilising calcium from the bones This mechanism accentuates the osteoporosis of rickets, but tends to prevent tetany by maintaining an adequate serum calcium level However where the bones have been excessively depleted of their calcium, tetany is seen as a complication both in rickets and in osteomalacia.

[illegible] and also causes apparent stunting of stature

The anterior fontanelle in infants frequently remains wide open long after its normal time of closure and bossing of the frontal and perietal bones is commonly seen. In young infants with severe rickets there may be extreme thinning or 'craniotabes' of the occipital and perietal bones

The softened long bones develop curvatures and may even fracture spontaneously Epiphysial enlargements are commonly seen in wrists and ankles and in severe cases also in the fingers The X ray appearances are characteristic and are most often seen at the distal epiphysis of the ulna and femur as fuzzy, irregular concave junctions Cupping may be seen at the distal ends of long bones The pelvis may be flattened, or the pubic arches may be pushed in to produce a 'tri radiate' pelvis. Dentition is usually delayed and the teeth may show defective calcification

The general musculature in rickets is typically hypotonic and on this account, affected infants are usually fat and flabby and are late in sitting up, crawling or walking They

are prone to develop the characteristic 'pot belly' Tetany is likely to occur in severe cases when the serum calcium falls below 6 mgm per 100 ccm. Nutritional microcytic hypochromic anæmia is common and infants tend to suffer from frequent gastro intestinal disorders The liver and spleen are usually palpable

In osteomalacia patients generally complain of pain and aching in the bones, either local or generalized Weakness is usually marked and severe tetany commonly occurs There is an exacerbation of symptoms during pregnancy and lactation but in intervals between pregnancies the disease is quiescent Gross and progressive skeletal deformities especially of the pelvis thorax spine and long bones may result The pelvic deformities may make labour difficult or may even make parturition impossible

(3) Diagnosis

Diagnosis can be made on clinical radiological and biochemical grounds In early cases where bony changes are not marked X rays will be helpful (generalised osteoporosis and vertebrae show biconcave deformity) Estimation of serum calcium and phosphorous (which are low) and serum phosphatase (which is much increased) give indication of its presence In case of osteomalacia deformities of lower limbs the thorax and the spine give indication of endemic areas Differential diagnosis from other osteoporot c diseases *e g* hyperparathyroidism is made by blood examination the serum calcium in the latter condition is high the phosphorous is low and phosphatase above normal levels.

(4) *Prophylaxis and Treatment*

Rickets can be prevented in infants by proper feeding regular exposure of the body to sunlight (ultra violet rays) or addition of vitamin D to the diet from an early age In countries where adequate sunshine is lacking vitamin D (in form of cod liver oil or as halibut liver oil or calceferol) should be given to all infants between the ages of 3 months and 2 years Concentrates are preferable to cod liver oil if there is fat intolerance as in coeliac disease In tropical climates the causal factor is usually a lack of calcium in the mothers diet Thus during pregnancy specially during later months, mother's diet should be supplemented by adequate amounts of milk along with vitamin D and calcium.

Curative treatment is based on similar lines Where the disease is active daily doses of 2 to 3 thousand units of vitamin D rapidly effect a cure Exposure of the infant for a few hours to sunlight daily is necessary If not possible ultra violet rays exposure may be given It is started with two minutes daily, with the lamp at a distance of three feet from the body, alternately to the back and front The duration of exposure is gradually extended to about 15 to 30 minutes Bony deformities may require proper treatment, such as splintage or even osteotomy

Treatment of osteomalacia can only prevent further bony deformities and [illegible] alcium and phosphorous [illegible] 10 000 to 50 000 units of vitamin D daily [illegible] ry preparations are the forms in which it is usually given

Prognosis—This is good as regards life though the infants are likely to get secondary infections which may prove fatal Deformities gradually become less marked with growth of the child

Renal Rickets—This is a rare condition of defective calcification of bones associated with chronic renal disease One form resembles rickets and the other is due to hyperplasia of parathyroids

7. Scurvy

Scurvy is a deficiency disease caused by inadequate intake of vitamin C in the diet It is characterised by anæmia great debility, tendency to hæmorrhages

and softening and fragility of bones It appears that advanced liver disease may also produce scurvy by interfering with the utilization of vitamin C The disease i
regions,
amount c

Vitamin C is easily synthesized and the synthetic product which is called ascorbic acid or cevitamic acid, is much cheaper than the natural product Vitamin C plays a vital part in the maintenance of the intercellular substance of the body connective tissues, and thus particularly helps to maintain the formation of bones teeth, cartillage and fibrous tissue in a healthy state It has been demonstrated that a vitamin C deficient diet causes a marked reduction of the plasma vitamin C content, and a significant reduction in the amounts daily excreted in the urine A daily urinary excretion of 13 mgm is the lower limit of normal, and that an output of 40 mgm implies that the patient is saturated with vitamin C. The normal range of vitamin C in the plasma in fasting individuals varies from a minimum of about 0.6 mgm to a maximum of 1.5 to 2 mgm per 100 ccm It is
n) The bodily requirements of vitamin
ism, thus infants and growing children
es and the body requires considerably

Saturation test—If a healthy adult on diet with fruit takes a large dose of ascorbic acid (500 to 1000 mgm) on successive days, he excretes in his urine nearly the whole of it in the first 24 hours and the whole of the second dose in next 24 hours Patients with scurvy and those on deficient diet do not start to excrete even half the daily dose until more than 2000 mgm have been ingested The tissue probably take up ascorbic acid till saturation point is reached while this is taking place only small quantities (8 to 12 mgm) are excreted daily in the urine An intradermal test has been devised to determine whether the patients' diet is deficient in ascorbic acid. 0.01 ccm of a sterile solution containing 2 mgm of indophenol in 40 ccm of distilled water is given intradermally If time taken for the colour to fade is more than 10 minutes, the diet is probably deficient

Scurvy occurred in old days among sailors who lived on salt meat and biscuits for prolonged periods during sea voyages. Besides deficiency of vitamin C there was probably deficiency of vitamin A, thiamine and possibly other vitamins also

(1) Pathology

The basic lesion in scurvy is degeneration of the intercellular cement substance or collagen of the connective tissues Damage to endothelial cells of the capillaries produce the characteristic hæmorrhages of scurvy The bones and teeth are softened, and sub-periostial hæmorrhages (especially of femur and tibia) are characteristic particularly in children

The skin is pale and dotted with hæmorrhages varying in size from pin point to large ecchymoses the lower limbs and in infants the inner aspects of the thighs are common sites The mucous membrane of the gastro-intestinal tract is congested and ulceration may occur in the stomach and intestines profuse and fatal hæmorrhages may take place The heart is hypertrophied and dilated and sudden deaths may occur on exertion Anasarca is present, liver and kidneys are congested Fractures commonly occur and are slow to unite and form large callus Separation of epiphyses and beading of ribs commonly occur In experimental animals fatty marrow of the long bones is replaced by red hæmatogenous marrow The blood shows anæmia with normoblasts and macroblasts in large numbers Administration of ascorbic acid rapidly produces reticulocytosis, increases red cells and hæmoglobin

(2) Clinical aspects

Experiments show that in man depletion period of ascorbic acid from the body on a deficient diet before typical symptoms of scurvy appear is 4 to 7 months Before this there is a period of subclinical scurvy in which such symptoms as debility, diminished resistance to infection imperfect healing of wounds, etc are observed. This is called the sub-scurvy stage and in this condition the patient is in an unsaturated state.

In childhood if ascorbic acid is completely absent from diet, symptoms of scurvy appear in 4 to 6 weeks, if small quantities are present in diet it will take longer The onset of scurvy is insidious in children, the skin becomes sallow and mucous membrane

pale The child lies in the bed quietly with hips and knees half flexed movement give rise to pain, tenderness is due to hæmorrhage in muscles or under the periosteum or epiphysial area Fever rarely above 101° may be present

(3) Symptomatology

In adults early symptoms are loss of appetite weakness breathlessness on exertion
lethargy and dizziness Later peticheal
or large ecchymoses may be seen on any
n and dysentery may be associated with
to muscles may appear and such muscles
he affected limbs resent movement and
in infants *and children Hæmorrhages*
in the retina, brain, spinal cord, intestines or any other organ, may produce a variety of lesions and symptoms

Changes in the gums present early and one of the most characteristic features of the disease At first fungus elevations or *scurvy buds* appear between the teeth and these gradually extend till the whole gums may be generally swollen, spongy and bleed on the slightest touch These swellings may later break down and ulcerate, and the teeth may loosen and fall out, the patient cannot masticate his food The breath is foul and *offensive*

Anæmia is common and is caused by blood loss and by interference with the activity of the bone marrow The complexion is muddy and there is increased pigmentation of the skin.

(4) Diagnosis

of the gums teeth peticheal haemorrhages and ecchymoses
make the diagnosis evident In milder cases and
lood ascorbic acid levels and of excretion in the
resistance test is also valuable and is performed
the arm and inflating it to a pressure
pressure of the patient It is maintained
The number of petichæ on the forearm
4 cm below the bend of the elbow are
idicating capillary damage

Purpura and subcutaneous hæmorrhage due to leukæmia or thrombocytopenia are differentiated by making a leucocyte count and estimation of platelets and determining the bleeding time

Complications—Pneumonia is a frequent complication which may be fatal Infectious diseases *such as dysentery malaria typhoid may occur*

(5) Treatment

The bodily daily requirement of vitamin C is about 25 mgm and diets containing at least this minimal amount, would be sufficient to prevent scurvy All the symptoms of scurvy usually respond rapidly to treatment with an adequate diet
200 mgm of vitamin C
This amount
pounds) *of fresh*
oranges Raw
in C but on account
of risk of tape
be used Synthetic
ascorbic acid *may also be given* in dosage of
mgm daily by mouth,
severe cases 1 000 mgm or more may be given per day In acute cases

to be

gastı
postı

tion but it is however, very likely that the healing of such ulcers may be hampered or delayed by a vitamin C deficiency It appears reasonable to suggest that all cases of peptic ulceration should be given adequate amounts of vitamin C. What applies to peptic ulcers applies to wounds and ulcers in the body generally, as healing processes are essentially based on fibroblast activity Some eminent authorities suggest that administration of vitamin should be made a routine in the treatment of all cases of gastric and duodenal ulcers They recommend that 1 000 mgm of ascorbic acid should be given on 3 consecutive days to each new patient to saturate the body, and thereafter 25 mgm should be given daily preferably in the form of fruit juice

The body requirements are also increased during infections and fevers and fruit juices should be given in all illnesses

(6) Prognosis

Prognosis is good if the diet is changed and the patient is put on proper treatment, all cases recover Otherwise it is bad Susceptibility to scurvy varies and all persons on the same deficient diet do not develop scurvy at the same time This is probably due to the fact that some hold ascorbic acid in the tissues better than others

(7) Prophylaxis

This depends on the fact that a person should get at least 50 mgm of ascorbic acid daily in his diet This amount is supplied by 100 gm of fresh oranges, lemons or grape fruit Bottled lime juice is not much good

8 Sprue (also known as Psilosis, Ceylone Sore mouth)

(1) Introductory and General

Sprue is a chronic, afebrile diarrhœal disease caused by functional impairment of the absorptive power of the small intestines resulting in the deficient absorption of fats vitamins and other essential substances in the food The prominent symptoms are the passage of large, frothy white stools flatulence progressive emaciation soreness of the tongue and a rogressive anæmia of the pernicious type The disease chiefly affects Europeans esident in hot damp tropical countries, though recently a number of cases have en reported in people who have never been to the tropics The writer has n cases of sprue among the inhabitants of northern India During World ar II Elder (1944) and Leishman (1945) observed a mysterious malady ch afflicted Indian troops in the north eastern zone to which the name rasmic syndrome was given and which was indistinguishable from sprue The on of occurrance of cases was March to September with its peak in June The ers who suffered were mostly those living under good conditions Manson (1941) obtained history of dysentery in 40 per cent of the cases but in cases it was met with only in 9 per cent of cases In most of the cases ndrome was fully established within two months of diarrhœa starting loss ght was the outstanding feature

estion in sprue is usually normal but there is deficient absorption of fatty acids ose and it is these unabsorbed constituents which cause the typical bulky gaseous, ols Absorption of vitamins hæmatin c factor and calcium salts is interfered may produce a variety of deficiency symptoms The disease is more common s than males it generally occurs in middle age but cases occur even in children usually occurs during the rainy season

) Aetiology

sential cause of sprue is still not understood The disease is not caus t Scott (1923) considered that calcium and parathyroid defic

this disease, but it has been shown that a calcium deficiency is the result and not the cause of the disease

A numben of writers have strongly supported the infection theory, but the apyrexial [illegible]

It has been suggested that the basic *defects* viz, *loss of ability to absorb fatty acids*, glycerol and glucose, is due to failure of phosphorylation and the loss of phosphorous due to failure of phospholipid formation Napier (1943) considers that sprue is caused by an inborn error of metabolism which normally remains latent but becomes patent *when the organism is subjected to certain strains and stresses especially those associated* with tropical residence. The nature of disease is far more that of a metabolic disorder than an infection This error of metabolism leads to primarily a failure of absorption in the small intestines, of fats vitamins and minerals and to a less extent of carbohydrates *and produces all the symptoms of this disease*

(3) Pathology

No characteristic pathological changes are found All the tissues such as muscle are wasted and all the internal organs especially heart liver, spleen are atrophied In advanced stages the bone marrow shows the [illegible] changes found in microcytic anæmia, later the marrow may be [illegible] active hæmopoietic tissue The intestines show thin [illegible] of the valvulae conniventes and thinning of the [illegible] the intestines to be morphologically normal (in autopsies)

Opaque meal shows that the mucosal marking in the duodenum and Jejunum are coarser and disturbed, the bowel is full of gas, the meal is distributed in segments of the gut isolated in distended coils on account of disturbance of motor activity which is the result of deficiency states The passage of meal through the gut is irregular and delayed, the peristalsis is inhibited

(4) Clinical aspects

The onset of the disease is usually insidious In most of the cases three cardinal symptoms—diarrhœa flatulent indigestion and sore tongue and mouth are present when the disease is fully established These may appear simultaneously or one after the other in any order Soreness of mouth often preceeds diarrhoea Skin changes may occur and are of two types—follicular hyperkeratosis and parakeratosis Well marked skin pigmentation especially of the face occurs in some cases

In the early stages diarrhoea may be intermittent and mild The diarrhœa is of two types acute and chronic, *in the former the stools are watery Generally after food* which disagrees the abdomen becomes distended with gas there is gurgling and a liquid stool with much gas is passed giving much relief There is no pain or tenesmus Three *or four* such stools may occur, in the course of the day This has been termed as 'pre sprue' stage by some The acute stage passes off and is *followed* by chronic sprue stools which become pasty, light yellow or clay coloured or white frothy and bulky in appearance and with a foul smell There may be only one stool early in the morning but often there are several in the day Microscopically the appearance of the stool is normal except that there is much fat and crystals of *fatty acids In sprue* the reduction of the normal stool pigment is a classical feature and all cases at some stage or other have passed pale stools

Flatulence always occurs It is at first mild and intermittent and may be relieved by passage of stools It gradually gets increasingly severe and may cause destressing painful and persistent abdominal distention which is most troublesome in the latter part of the day and attaining its maximum in the evening The soreness of the mouth increases, *the tongue and buccal mucosa may develop small apthous ulcers*, later the tongue becomes red acutely inflammed and denuded Salivation may be troublesome The buccal lesions may extend downwards into the pharynx and oesophagus and swallowing may be very painful and even dysphagia may occur

The disease usually progresses by spontaneous remissions followed by increasingly severe relapses The patient gets extremely emaciated and mentally depressed Anæmia sets in after diarrhoea has lasted for sometime Anæmia is at first of the hypochromic microcytic type but later of hyperchromic macrocytic type indistinguishable from pernicious anæmia rapidly develops The red cell may fall from two to one million per cmm This is manifested by increasing weakness prostration, disinclination for exertion and other symptoms of anæmia. The patient becomes progressively emaciated from lack of absorption from the gut and consequent starvation The blood pressure is low (90 to 100 mm) and basal metabolic rate of minus 10 to 20 Nervous symptoms referable to subacute combined degeneration of the spinal cord may become manifest The blood calcium is low and if severe tetany may develop Symptoms of various vitamin deficiency states may become evident

(5) Diagnosis

The diagnosis presents little difficulty once it is realised that dysentery is not the only cause of diarrhœa in the tropics The characteristic combination of steatorrhea glossitis and a macrocytic anæmia makes the diagnosis easy In the stools there is a large excess of fat The blood calcium may be low and the glucose tolerance test gives a flat blood sugar curve due to delayed and defective absorption

Gastric analysis often shows hypochlorhydria or achlorhydria with response to histamin More than half of the cases have acid curves at least within normal limits Presence of hydrochloric acid in stomach distinguishes it from pernicious anæmia Also there is no jaundice in sprue while in pernicious anæmia the skin is lemon yellow in colour

Hypoprotinaemia is common especially in advanced cases Sprue is distinguished from pellagra by the fact that there are no cutaneous manifestations and steatorrhea

(6) Treatment

In the treatment of sprue utmost care lies in procuring bodily rest and selecting a very careful dietary for the patient It is to be understood that sprue is a disease in which the gastro-intestinal tract bears the greatest brunt of attack Hence if the treatment of the case is begun early in the disease by careful regulation of the diet very successful results are obtained while if it is undertaken too late in the period when the absorbing surface of the intestine is damaged the results are discouraging The treatment must be thorough and persistent It should be realised that carefully adjusted diet does little more than rid the bowel of a mass of material it is unable to absorb The deficiency syndrome can only be corrected by administering vitamin preparations and liver extract Food should however be given by the mouth in form of diet rich in proteins and adequate in calories This requires considerable efforts on the part of nursing staff since patients have lost all appetite and desire for food In fact the treatment depends entirely on intensive liver therapy While refined liver extracts are effective in pernicious anæmia they have relatively little value in sprue Crude extract may be given by the mouth in mild cases but injections are preferred Very much larger doses of crude extracts have to be given than are given in pernicious anæmia It is advisable to give 5 ccm every other day or every day in the first week or two of treatment till the patient shows marked signs of improvement The dose is then reduced to 5 ccm twice a week till he completely recovers After the acute symptoms are controlled liver extract in doses of 5 ccm weekly may have to be continued for months or years before it can be stopped altogether In very serious cases with marked degree of anæmia a blood transfusion of 500 ccm of whole blood should be given and if necessary repeated

The diet during treatment should be low in carbohydrates and fats and high in proteins Meats are well bourne and should be given in the beginning and later carbohydrates are introduced in form of potatoes and other starchy vegetables Later fruit and vegetables are given in small quantities and

legs and loins heavy, there is dragging of the legs and more or less inability to walk. Later, there may be extreme spasticity and rigidity of the leg muscles, the case may progress to such a condition that he can only move his hands and feet in a sitting posture. Sensory disturbances are not generally evident. The sexual power is said to be enfeebled but the mind speech and pupils escape.

The physical signs are those of typical spastic paraplegia with exaggerated knee and ankle jerks ankle and patellar clonus and an extenser plantar response. The gait depends on the degree of involvement of the spinal tracts. At first the attitude of the legs is one of extension with adduction the patient walking on tiptoe the body is raised high before the toes leave the ground giving rise to up and down movement of the shoulders and progression is affected by tilting the pelvis and circumducting the legs. The legs may be crossed scissors wise. The more feeble patients use one or two long sticks for support in walking. Later paraplegia develops and in the final stage walking is impossible. Progression is then made by crawling on the balls of the toes and on the hands which are often supported by wooden sandals. In most cases the trunk and upper limbs are unaffected.

The disease runs a very chronic course. Degeneration being limited to the motor tract is not a direct danger to life. It may be arrested but there is not any possibility of cure in the sense of restoration to the previous condition of health. The degree of paralysis produced by the original attack remains permanent.

(4) Diagnosis

Diagnosis is made clinically together with the dietetic history. The disease must be differentiated from other causes of spastic paraplegia such as syphilitic myelitis spinal caries subacute combined degeneration of the cord amyotrophic lateral sclerosis and syringomyelia.

(5) Treatment

There is no cure for this disease as the changes produced in the cord are permanent. Jacoby (I M G, 1945, Page 246) has, however, obtained successful results in a small series of cases with prostigmin which is the synthetic equivalent of the alkaloid physostigmin. He injected 0 5 mgm of prostigmin methyl sulphate in 1 ccm of water intramuscularly every day in series of 14 patients. Of these 8 patients who received 12 injections each improved considerably. All pains disappeared. The muscular rigidity and spasm in the lower limbs were relieved. Three cases improved and could walk but had ataxia on closing their eyes the pains disappeared. Three cases did not improve at all. Jacoby considers that in lathyrism the anatomical functional lesion is in the upper motor neurons of the pyramidal tract, there is imbalance between the production and destruction of acetylcholine thus interfering with the transmission of co ordinated nervous impulses in the tract and producing the symptoms of lathyrism. Prostigmin acts by protecting acetylcholin against destruction and the impulses thus become co ordinated.

The *prevention of the disease* depends on the improvement of the economic condition of these people and abolition of the system of bondage that exists in some states of India at present. Howard suggests that *khesari dal* should be planted in drills and the contaminating *Vicia sativus* removed by weeding. This should be done not only in places where lathyrism is rife but also in those areas from where the imported grain is sent to the famine stricken areas. But in view of the divergent views on the part played by vicia in the spread of the disease, no successful measures can yet be devised. Nourishing diet is obviously of value. There is no specific treatment. The paralysed parts should be kept warm, massage and electricity are indicated.

CHAPTER XI

CLIMATE, WEATHER AND MAN

THE INDIVIDUAL AND HIS ENVIRONMENT PHYSIOLOGICAL EQUILIBRIUM, MECHANISM OF ADAPTATION, ATMOSPHERIC ENVIRONMENT—CLIMATE AND THE INDIVIDUAL EFFECT OF HEAT AND SUNLIGHT IN THE TROPICS, EFFECTS ON THE DIGESTIVE SYSTEM, EFFECTS ON THE RESPIRATORY AND CARDIOVASCULAR SYSTEMS EFFECTS ON THE NERVOUS SYSTEM, EFFECTS ON THE ENDOCRINE SYSTEM AND GROWTH BASAL METABOLISM IN THE TROPICS—TROPICAL CLIMATE AND RESISTANCE TO INFECTION—CLIMATE HEALTH AND DISEASE TELLURAL INFLUENCE—TROPICAL NEURASTHENIA AETIOLOGY AND INCIDENCE TREATMENT

Reaction of Body to Climate

Introduction

Though physiology in its widest sense signifies the study of the phenomena presented by all living organisms, its chief interest is centred round the body of man It should therefore be the objective of human physiology to study the so called 'normal human individual' since it provides an essential base line for the study of disease The definition

1. The Individual and his Environment

Historical

The study of the individual in relation to his environment has recently engaged the attention of many a physiologist and clinician though the problem is by no means a new one In the earliest days of medicine in India centuries before the Christian era the Hindu physician *Charaka* drew attention to the effects of different 'airs' and places on mankind He prescribed special diet for p
food for the summer and anoth
Hippocrates recognized not only
logical implications The intere
science of bacteriology made it[illegible] the pioneer researches of Pasteur Lister and others In the study of diseases, emphasis was laid more on the invading parasite than on the invaded individual With the advent of the science of immunology serotherapy and chemotherapy, the importance of environmental influence receded more and more into the background Though the interest of medicine at present is chiefly centred, and perhaps rightly, on [illegible]

Reactions to environment

is none the less important
Two methods have been dev
It seeks to lessen the impac
endeavour to prevent disturba
the consumption of energy (
phenomenon of attempting
formation and in the variou
organisms, the same reactio
deposition of subcutaneous f
native is that the organism becomes more *reactive* and instead of resisting any force disturbin
that they
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man is
and later to control that environment itself'

(1) Physiological Equilibrium

External and Internal Environment

[illegible] cts of which we are concerned is not in reality [illegible] well known though the external environment [illegible] remarkably constant and this is achieved [illegible] factors inherent in the saline fluids which [illegible] *milieu interne'* of Claude Bernard, and [illegible] lesigned to prevent abnormality The extent [illegible] brought into play by adverse changes in the

environment of the individual and the degree of their response are measures of the organism's reserve capacity or power of adaptation On this reserve power depends the success of the individual in his adaptation or acclimatization to changed surroundings and environments

(2) Mechanism of Adaptation

Adaptation has been aptly defined as the continuous adjustment of internal relations to external relations The ability to respond actively to changes in environment is an essential characteristic of any organism The range of environmental adaptation of even the most primitive cell is relatively wide although the mechanism of response may, be simple, but as we advance in the scale of animal life the range of adaptation becomes even greater as the mechanism and the means of adjustment become more complex The higher we ascend in the animal scale, the means by which ... and an ... For this ... etc and ... reason is ... alteration, made or threatened can be recognized and guarded against, in other words the adaptive reactions become conscious and adjustment to meet them 'volitional All the reactions of a biologic mechanism to environment may be said to be mediated through three distinct *but mutually related and integrated processes—chemical endocrinal and nervous. The three* components are functionally inseparable and no one component can be disturbed without disturbing the others.

The ability to maintain an equilibrium without the breakdown of the adaptive mechanism under *adverse conditions determines the development of the individual and ultimately of* the species. The greater the possibility of protective reaction the greater are the chances of survival It seems important therefore to stress the fact that the animal body although often compared with a man made engine differs fundamentally from the latter in that it has latent reserve forces capable of adjusting the animal to a new environment in other words it possesses powers of adaptability These forces call forth hypertrophy of glands and tissues in response to appropriate stimuli and even carry out repair of damaged parts Sensibility or facility of response can be improved by frequent usage or 'training' as in the case of muscular exercise. The athlete can undertake a given amount of exercise with less disturbance of respiration and circulation than can the untrained person and his return to the resting normal condition is also quicker

(3) Atmospheric Environment

... As the ... he part it ... mals We ... ood. The ... rom place ... luctuations ... *differences*

The term climate has been defined as the combined effects of the sun the atmosphere and the earth upon living objects at any one place on the earth's surface. Climate primarily results from the effects on the earth s surface of *the incident solar energy and its unequal* distribution The climatic elements temperature humidity etc are dependent on physiographic factors such as distribution of land and water, mountain ranges nature of soil distance from the equator and height above the sea level The latitude and the altitude are however, the most important and deserve special attention

The words climate' and 'weather' are often used synonymously in common parlance but 'weather means those atmospheric elements we see feel or observe at a particular time or specified period while climate means the aggregate of weather conditions In cold and temperate latitudes the weather becomes a more outstanding feature than the climate itself *In the tropics for the greater part of the year,* the climate becomes a succession of equal combinations of meteorological elements the annual range of which seldom exceeds the diurnal range The 'weather' in the tropics therefore is practically the same as the 'climate The monotony of the tropical climate is a characteristic not seen in the temperate or cold regions of the globe

Tropical climates

It is generally assumed that the climates of the whole of the tropical zone are in all respects alike and therefore the term 'tropical climate' is often used, though incorrectly Climatologists have divided the tropical belt into several subdivisions according to the situation of the land in relation to the equator, the vicinity of water, the growth of vegetation, the presence of mountains or hills, the proximity of land to oceanic currents and trade winds, and its height above the sea level All these factors will naturally influence the 'climatic type' of a locality Thus the tropical zone includes deserts damp forests, jungles swamp lands and fertile islands refreshed by cool steady winds from the ocean, low lying plains and valleys under the influence of the periodic monsoons, and [illegible] several thousand feet above sea level All these regions are not equally disagree- [illegible] free from many tropical diseases [illegible]

agreeable. [illegible] with peculiar climatic types with their special advantages [illegible]

The climate in tropical plains varies but little and the temperature ranges between 75°F (25°C) to about 115°F (46°C) There are no seasons in the tropical zone and monthly and diurnal variations of temperature are slight. These areas are often subject to the influence of monsoon with their alternate dry and wet spells. They are usually very fertile and support a variety of luxuriant vegetation A large portion of the plains of India has a climate of this type and therefore it is of very great interest to us to know the physio logical adjustments required of human beings in such a climate

2. Climate and the Individual

The influence of climate on man is so well recognized that it is often the main topic of daily conversation One often hears of a 'bracing' climate or a 'relaxing' climate, [illegible] expression in our desire for a 'change [illegible] the physical and mental vitality [illegible] Climate' puts [illegible]

Climate and Civilisation

[illegible] ere is also a distinct optimum [illegible] any departure from it adversely affects the organism.

(1) Effect of heat and sunlight in the Tropics

In considering the effects of residence in tropical climates attention is at once directed to three major environmental factors, *viz*, temperature, humidity and sunlight There are a number of other climatic and environmental factors such as wind movement atmos pheric electricity, ionization, etc, which also affect the human organism though the responses elicited do not leave lasting impressions on the individual In nature, all these climatic factors operate simultaneously and the reactionary changes observed at any one time are in most cases a summation effect, one factor being superimposed on the other Thus while the acute effects of encountering very high temperatures as of a heat wave in a desert region may be tolerated without harm, the organism may show signs of intolerance or breakdown when excessive humidity is superimposed on such a high environmental temperature.

Sunlight

The biological effect of sunlight has received perhaps more attention than any other factor in this group A careful perusal of the literature shows that the knowledge gained [illegible] The beneficial results obtained by helio- [illegible] in the treatment of rickets [illegible] the spectrum was the im- [illegible] Several investigators in the [illegible] lands East Indies have adduced

experimental evidence indicating that the ultra violet light being nonabsorbable by the skin is probably much less important than the infra red and the visible red end of the spectrum, which penetrates the superficial layers of the skin and is perceived by the organism as heat energy Whatever direct effects tropical sunlight may have have therefore been attributed to its thermal action

The effect of humidity on the human organism has recently engaged the attention of public health authorities and sanitary engineers interested in environmental control through air-conditioning methods That humidity modifies to a great extent the effects of heat is generally recognized A moist humid atmosphere is associated with depression and discomfort and conversely dry air, irrespective of its temperature induces a feeling of comfort and well being The water content of the atmosphere must affect the water content of the body In the regions of high environmental temperature such as are met

Studies on the changes produced in the body of man as a result of exposure to high environmental temperature have been numerous but like most aspects of tropical physiology the data are conflicting. It has been reported that a change in the environmental temperature produces a change in the *body temperature* of the individual and that in the tropics body temperature may be permanently above the average in the temperate zones While it is true that a change in the body temperature of an individual may be easily effected for brief periods by exposure to high external temperatures it is doubtful if in view of the sensitive heat regulating mechanism in man a permanent change can be brought about by prolonged exposure such as residence in the tropics From physiological considerations it is logical to assume that the flushing of the skin as a result of exposure to a hot environment raises the skin temperature, but the temperature soon drops when perspiration breaks out

It was generally recognized that tropical races are at an advantage over the European settlers in the matter of heat dissipation The possibility suggested itself that acclimatization for generations in a climate where the mechanism of heat loss had to operate under excessive strain might have endowed the skin of the tropical races with an additional power and facility in getting rid of excess heat by the processes of physical heat regulation—conduction convection radiation and evaporation—at a more rapid rate than individuals from cooler zones It has been claimed that the skin of tropical races loses heat by convection more rapidly than the skin of white races but these conclusions have not been universally accepted The suggestion next put forward was that the dark skin radiated heat more quickly than the white skin but satisfactory evidence has not been obtained in favour of this contention There is little doubt that pigment plays an important part in heat regulation in other ways Pigmentation of the skin is necessary to protect the deeper structures from the injurious effect of sunlight and to protect the sensitive cutaneous nerve endings from irritation The brown skinned races in the tropics by virtue of the pigment have apparently developed a more sensitive cutaneous heat regulating mechanism and they can cool off more rapidly by reason of the early formation of a fine layer of sweat drops

For physical heat regulation however the activity of the sweat glands is of outstanding importance Their efficiency depends on several factors (1) humidity of the environmental air (2) concentration of sweat glands per unit area and (3) the degree of activity of these glands Humidity though it is important because on it depends the evaporation of water from the skin does not in actual practice exert a great influence because apparently high degrees of humidity provided they fall short of absolute saturation can be borne by the system with impunity The concentration of sweat glands in the skin may regulate the amount of perspiration and it was believed by many early workers that the better heat tolerance of the dark skinned races was probably due to this factor

A study of the composition of sweat produced in extreme dry heat shows that there *is an adaptive response* on the part of the organism and that the concentration of salt in sweat decreases after the first few days in the hot environment To cite a concrete example the amount of sweat produced with ordinary type of work in a climate such as that of Calcutta (95° to 105°F or 35° to 41°C) may be as much as 7 litres during the day Assuming a sodium chloride concentration of 0 3 per cent this means a loss of 22 5 gm of salt Man s daily intake of sodium chloride is 10 to 15 gm and since the average normal excretion of salt in the urine is in the neighbourhood of 12 gm in 24 hours

the degree to which muscular work in such a climate may deplete body chlorides is remarkable If this depletion is not compensated the normal acid base equilibrium of the body fluids is apt to be seriously disturbed and heat cramps from loss of salt may supervene It seems clear that some sort of adaptation takes place in normal healthy individuals Little is known, however, of the nature of this adaptation, though it has been noted that all men sweat more readily as they get accustomed to exposure to heat This increased 'ability to perspire' is known to be one of the few definite adaptations to high temperature and it is interesting to note that it is a case of 'controlled rather than profuse wasteful sweating The sweat secreted is said to contain an unusually low concentration of sodium chloride and this would appear to be an attempt at conservation of chlorides as even on a high chloride intake their concentration remains low

(2) Effects on the Digestive System

Atonia and stasis

It has frequently been observed by Europeans coming to the tropics that there is a [illegible] and a lessened desire for animal food Though this may [illegible] for animal [illegible] here is also [illegible]

[illegible] may be an expression of the greater need for gastro-intestinal [illegible] activity is normaly unduly accentuated

Gastric acidity

A general impression seems to prevail that the gastric acidity of rice eating Indians is lower than that of meat eating Europeans A fractional gastric analysis on a number of normal Indian male and female subjects showed that on the whole their gastric acidity was higher than in normal Europeans This is contrary to expectations, for hot climate and vegetarian diet are both believed to be factors that tend towards decreasing gastric acidity No explanation of this phenomenon is yet forthcoming

Bacterial flora

Bacteriologists have claimed that the bacterial flora in the intestines of inhabitants in the tropics are different from those of colder climes The bacterial flora of the lower intestinal tract vary with external temperatures and hence it is natural to expect a difference between those found in the tropics and the cooler regions As the nature of the food is also known to influence the relative proportions of the various bacterial [illegible] the intestinal flora and as the predominant dietary constituent in the tropical [illegible]

of effecting a complete turnover from a [illegible] persons fed on high protein diet, to a flora markedly simplified and Gram positive, inducing coincidently a change in the hydrogen ion concentration from nearly neutral to distinctly acid

Recent work [illegible] of *persons* living in Calcutt [illegible] e Bengalis is acid, those of [illegible] Although the Marwaris are [illegible] y *consume* very little rice [illegible] t the consumption of rice produces an acid reaction in the large intestine while wheat produces an alkaline reaction When Bengalis were [illegible] of the stools changed from acid to alka[illegible] the stools it was thought likely that acid[illegible] of Bengalis but surprisingly enough *Lact*[illegible]

(3) Effects on the Respiratory and Cardiovascular Systems

There is a good deal of divergence of opinion with regard to the effects of tropical climate on respiration The consensus of opinion appears to be that the rate is diminished but the depth, as indicated by measurements of the minute volume is increased. A slightly deeper breathing is more efficient for the individual economizes energy and, at the same time the increase in the volume of air breathed cools the system These changes in the rate and vital capacity are probably of a temporary nature evident only in the case of the white immigrants to the tropics, and are not apparent in the natives of the tropics

A slight decrease in the pulse rate and in systolic blood pressure is a very common finding in the tropics Mills (1936) has shown that people migrating from West Central Europe or Central North America to the tropics nearly always suffer a marked fall in blood pressure within a year or two even though no debilitating disease or infection has occurred Probably there is a slight decrease in blood pressure due to lowered vasomotor tone and a general slowing of physiologic activity in the high environmental temperature in the tropics but the changes are comparatively insignificant The increase in sweating which is necessary in the tropics must require a constantly increased blood supply to the skin, and has been estimated to be as much as 50 times of the amount in temperate climes The immediate result, if the total volume remains constant would mean relative anæmia of the splanchnic region and the vital organs in the abdomen To counteract such circulatory disturbances there is usually an increase in the total blood volume.

The pale complexion of the white races migrating to the tropics has been frequently referred to as an indication of anæmia or 'thinness of blood Most authorities are of opinion however that a tropical climate *per se* does not produce true anæmia Several workers in the Dutch East Indies found that the values for red blood cells and the hæmoglobin lay more or less within the same limits for the white sojourner and the native resident of the tropics In two series of normal healthy Indians consisting of 50 and 30 individuals the mean hæmoglobin contents were found to be 14.77 gm and 15.70 gm respectively With regard to the number of red cells the average figures obtained in the Calcutta series were 5,533,000 and 5,362,000 and the mean of the Bombay series was 5,110,000 These figures are again above the classical 5,000,000

Most hæmatologists in the tropics appear to agree that the white blood cells are generally decreased though the change is not very great. As a rule the polynuclears have been found reduced and the Arneth count shifted to the left. This has been fully confirmed by workers in Iraq and in Calcutta It was found that the number of leucocytes if it differed at all was slightly lower than in temperate climates but the eosinophile percentage was definitely higher In 50 normal city dwelling Indians who had no heavy helminth infections the mean eosinophile percentage was nearly 7.0 Not only is the normal eosinophile count of the Indian high but in disease the eosinophilia tends to attain a very much higher proportion than in the Europeans in temperate climates *e g* 60 to 80 per cent eosinophilia is not uncommon in asthma and other conditions

It is not possible in the present state of our knowledge to explain the significance of the different hæmatological responses observed in the tropical races From the findings of various workers it seems reasonable to conclude that, far from interfering with the functions of the erythropoietic organs the tropical climate may actually exert some stimulating action on these organs The possible bearing of the low average white cell count on the defensive mechanism against disease processes requires further investigation

There is little doubt that there is a more pronounced disturbance of water metabolism and water movement in the tropics than in temperate surroundings This will naturally be reflected in the water content of the blood A number of observers have

attempted to throw light on this important aspect of tropical adaptation by measurement of blood chloride concentration Sundstroem (1925) working in Australia found that the blood plasma was more concentrated than normal and richer in chloride content in a hot environment. A slight alkalosis has been reported particularly in persons of sedentary habits which can be removed by water intake and muscular exercise

The average concentration of serum proteins in the blood of Indians according to Chopra and Mukerji (1931) appears to be slightly lower than the accepted standard figures of Europeans, but the albumin g
regard to non protein nitrogen content
to be low in the tropics this will prc
constituents of the blood including chol
sugar apparently is not so much affecte
to be high in the tropics In view of
to produce an increase in blood sugar,
the tropics. Studies have shown however, that diabetes is more common in the temperate climes Serum calcium is appreciably increased probably as a result of excessive production of vitamin D from ergosterol due to the radiant energy of the tropical sun

(4) Effects on the Nervous System

That hot environment actually disturbs the psychological reactions of the individual

Neuralgia, locomotor ataxia and other painful diseases are always aggravated when it is damp, cold and windy The weather may influence the course of chronic psychosis and unfavourable conditions may exaggerate pre existing states of either depression or excitement.

The intense heat and the bright sunl ght of the

Irritability

natives

(5) Effects on the Endocrine System and Growth

It has often been observed that the endocrine glands may be disturbed in tropical climes The association of increased metabolism, high energy level and higher incidence of metabolic diseases in a cooler climate and a sluggish metabolism, a low energy level, decreased resistance to infection and lower incidence of metabolic diseases in a tropical climate are generally recognized and it is probable that all these factors are ultimately bound up with the question of the activity of the glands of internal secretion

Thyroid adrenal apparatus

Much athological, have been collected, indi
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workers to to changes in temperature. In the
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That the thyroid adrenal apparatus is concerned in the heat regulation of the body is *borne out by pathological evidence* Lessions of these glands are frequently accompanied by marked disturbance of heat regulation and conversely disturbances of heat regulation, as in fevers frequently produce lesions in these glands High temperatures are known to affect adrenalectomized animals more easily and frequently they die in a temperature which is not serious for the control animals exposed for the same *length of time* All these facts indicate that there is a lowered resistance to heat in adrenal insufficiency

These facts enable us to speculate on the close interrelationship that exists between heat regulation and the thyroid adrenal system and which afford a physiological basis for the study of the *problem of the influence of climate on man It has often been noted* that a warm moist climate with little change from day to day is 'relaxing' This might be the result of [illegible] through it the sympathetic sy [illegible] associated with increased activit [illegible] these endocrine organs and the [illegible] ands of internal secretion (especi [illegible] ism responds to weather stimulat [illegible] between climate and health Wh [illegible] as tuberculosis *increased by a* [illegible] *n air treatment,* hydrotherapy an [illegible] those measures are beneficial which stimulate the thyroid adrenal apparatus without exhausting it and [illegible] defence of the organism against bacterial infections [illegible] nate weakens resistance against infections not [illegible] ve thought, but on account of the continued [illegible] and the sympathetic apparatus

It has often been stated that girls in tropical and subtropical regions menstruate at a comparatively early age It is also a well known fact that women marry and bear children earlier in warmer countries than in cooler regions These facts have led to the belief that the tropical climate induces premature sex maturity There is however no direct proof of this as no reliable statistics are available In India, various ages, ranging mostly between twelve and thirteen years have been given for the onset of menstruation. These figures are probably derived from observations on the time of motherhood. The mean age for the beginning of menstruation is 15 to 16 years among the negroes on plantations in Jamaica and Barbados

(6) Basal Metabolism in the Tropics

The question of the influence of climate on the basal metabolism of the individual is an important subject No satisfactory evaluation of the effect of the climate on metabolism however, is possible even to day in view of the wide divergency in the results *recorded* A review of the work carried out in tropical and subtropical regions in different parts of the world shows discordant results Some observers have thought that the basal metabolic rate is lower in the tropics Bose (1934) carried out a large number of observations by the Sanborn technique at the School of Tropical Medicine and came to the conclusion that the basal metabolic rate of healthy normal Indians living mostly on a mixed diet does not differ *materially from the accepted standards of Europeans and* Americans

Taking a general view of the whole problem it would appear that the observations of the majority of the workers who studied metabolism in the tropics are in agreement that there is either a slight decrease or no significant difference in the basal *heat production* in people living in the tropics as compared with the inhabitants of the cold or temperate regions It seems inconceivable that such a fundamental factor as basal metabolism should be affected by climate to any great extent any more than the body temperature

3. Tropical Climate and Resistance to Infection

We have so far considered the effect of tropical climate on the individual involving chemical physiological and psychical reactions It would be interesting now to examine [illegible] membranes of the throat, [illegible] f the body It is possible [illegible] of the organism but also affect the pabulum o [illegible] n any way affecting the bacteria themselves This brings us to the question of environment and host resistance the importance of which from the epidemiological point of view cannot be over rated. It

recognized the influence of climatic variations and have more than once shown the association of climatic fluctuation with asthmatic attacks Evidence has also accumulated which show the seasonal fluctuations of stereptococci in the throat and the severity of attacks of rheumatism and rheumatic arthritis More information however is needed to prove direct correlation between environmental features and naturally occurring infections of the respiratory passages

It has been suggested that ultra violet irradiation of the body, which is naturally obtainable in the tropics has the power of increasing resistance to infections A number of workers have demonstrated a temporary increase in the bactericidal power of the blood as the result of exposure to ultra violet rays This view is however not universally accepted A careful study of the frequency of colds *among irradiated and unirradiated* groups of volunteers at Johns Hopkins Hospital has definitely shown that resistance to infection is not altered by irradiation

It is not proposed here to enter into the field of immunity reactions and immune bodies in relationship to climatic ch ... immune bodies will change with the alterations in the ... The Report of the New York State Commission ... rabbits maintained at a temperature of 86°F (30°C ... ation of hæmolysins and reduced agglutinating powe ... kept at 68°F (20°C) It has been recently shown th ... dy temperature is raised to above 104°F (40°C) *agglutinins and bacteriolytic substances are produced in greater* quantities than in control animals kept at room temperature

A few words may be said about hypersensitiveness and allergy in the tropics as the phenomenon is closely associated with resistance to infection The Indian tribes of America suffered much less from allergic diseases and were much less susceptible to experimental serum disease than the white races Acton and Dharmendra (1933) pointed out the rarity of asthma of allergic origin amongst Indians The reason for this lower incidence is not known and will remain unanswered until the true nature of allergy is known There is evidence both experimental and clinical that hypo-adrenia plays an important role in the production of allergy It has also been claimed that slight changes ... *of the body might give rise to profound changes in the reactions* ... ult It has been shown for example that a shift of ... e alkaline side greatly increases sensitiveness in certain ... that hypo adrenia might well be brought about as a result of tropical heat ... hypothesis is accepted, a higher incidence of allergy in the tropics would be expected

4. Climate, Health and Disease

The climate of any country, can and usually does, exert a profound influence on its inhabitants The climatic factors often have a direct bearing on the health To begin with, the climate of a place very largely determines the food supply available to the people, and this not only affects the general health and well being of the people, but may also result in the prevalence of certain type of nutritional diseases *e g*, beri beri in the rice growing regions, and pellagra in the maize growing areas *Certain types of climates favour the prevalence of* particular types of insect life which may be responsible for the spread of insect bourne diseases such as malaria yellow fever, sleeping sickness, etc Bacteria ...

spread of ...
intense fo ...
others occur in a milder form

Diseases such as rickets are common in northern countries where the ultraviolet rays of sun light are not so plentiful, but are rare in tropical countries In the tropics on the other hand cases of heat stroke are common It has also been observed that diseases such as syphilis and gonorrhea run a very much milder course in tropical countries The neurological manifestations of syphilis

which are so crippling, are frequent in the temperate regions but are rarely seen in India Complications of gonorrhea such as urethral strictures, arthritis etc are comparatively much less frequent in the tropics

For a new comer into tropics, temperature of from 20-30°F above that experienced in temperate zones is in itself a considerable strain Individuals vary a good deal in their reaction to climate, and in every case the reactions produced in most cases are of a temporary nature The process by which man (or even animals and plants) adopt themselves to climates different to what they are used to is termed acclimatization In the period during which this transition is taking every effort should be made to lead a careful life and excesses of every kind, dietary exposure to sun etc should be avoided

Sunlight

Sunlight in the tropics is usually very intense, but apart from this it has no mysterious evil properties Special protection against the heat of the sun should be provided in the form of a proper headgear In India pugree is worn but a pith helmet is better as it protects the nape of neck and the eyes Best of all is an umbrella which not only protects the head but a large part of the body as well During very hot spells the sun ought to be avoided as much as possible but otherwise exposure to the sun specially in the cool morning period is beneficial New comers into the tropics should gradually accustom themselves to the climate and should be particularly careful with regard to exposure to the sun in the begining acclimatisation takes some time to develop

Clothing in the tropics should preferably be white in colour, as this absorbs the least of radiant heat The next best is pale blue or a light Khaki colour Black colours are the worst as they absorb heat The clothing worne should be loose textured to allow of free circulation of air, and loose fitting An open necked shirt and shorts or loose fitting trousers are quite satisfactory as are the shirt and dhoti, shirt and pyjama

Protection of the head and the spine is important especially if the individual has to be exposed to the direct rays of the sun in the course of his work For this purpose a hat with wide brims and a spine pad are desirable protections Lining of these with allumimum foil has been suggested Dark glasses should be worn to protect the eyes from glare

Attacks of diarrhœa may be caused by local chilling of the abdomen at night in summer, when sudden unexpected drops in temperature may occur A light woolen blanket or shawl should be wrapped round the trunk and abdomen especially in persons who have suffered from dysentery or other abdominal conditions Sitting under a fan after sweating should be avoided

Housing in the tropics

In those areas where intense dry heat prevails during summer, the ceilings of the rooms should be high and insulated if possible by being double with a free ventilation space between the two layers The walls may also advantageously be built double with a ventilation space in the middle They should be shaded from the direct sun by a wide verandah Thatched roofs are cooler than most other types but they harbour insects vermin etc. In single storied houses a very low plinth is desirable as it utilizes the cool reservoir of the ground to keep the floor cool In two storied buildings the lower story is much cooler during the daytime but the upper story is cooler and more airy by night In every hot weather it is best to close all the doors and windows during the day, but these should be opened wide in the evening

In damp climates where the temperatures never rise very high, houses should be built to provide the maximum amount of through ventilation Insulation of

the ceilings though not so important as in the drier climates is nevertheless desirable

Under ground rooms have long been used in places with hot dry summers and very cold winters The earth remains comparatively cool during the summer and helps to keep the air in such rooms cool and comfortable Cooling methods dependant on the evaporation of moisture such as the Khus Khus screens are placed in doorways facing the prevailing wind and are kept moist either with a spray or from an overhead tank dripping water A more modern version of this type consists of a large box which can be fitted into a doorway or a window On the outer side of the box is a khus khus screen kept moist by a drip from an overhead tank and on the inner side fitted into a circular opening is an electric exhaust fan which sucks air from outside through the khus khus screen and discharges it into the room Such an arrangement is remarkably effective and is very cheap to build and operate Such a system can be very economically and effectively adopted for use in hospital wards school dormitories and the like Besides providing the cooling it would have the further advantage of providing a clean dust free and insect proof atmosphere Invalids can also be comfortably taken by trains in the hottest weather by placing a cradle which is covered by a thick towel kept moist The patient is kept within the cradle with only the head exposed and an electric fan is turned on to the cradle

Great progress has been made in recent years in applying modern refrigeration methods to the air conditioning of living rooms offices operating theaters laboratories factories etc and a large variety of suitable plants are available These range from the small cabinet type of air conditioners which work off the ordinary household electric supply to the large conditioning units for factories with many acres of floor space These installations naturally involve heavy initial expenditure but their value in increasing the working efficiency and health of the inmates has been ampl [illegible] factories hospitals laboratories and schools is [illegible] equisite However where financial consideratior [illegible] installations there is still a great scope for extensive employment of the cheap and simpler devices based on moisture evaporation Artificially created cool atmospheric conditions will help to maintain better health and more efficiency from point of view of work Exaggerated fear of catching a chill when going in and out of air conditioned rooms is not justified The human body has a very large power of adoptation and when suddenly exposed to heat or cold the compensating mechanism is atonce set into motion and equilibrium is rapidly established The writer used an air-conditioned room in Calcutta for many years and never suffered from sudden change of temperature when entering or coming out of the room

The question of diet in the tropics has been fully discussed elsewhere In cold climates more food is required inorder to produce body heat In warm climates less food is required and certain articles of diet such as proteins and fats particularly should be cut down

Tellural Influence

Greval (1946) has described the telluric influence on disease and points out that the Indian soil is inimical to certain diseases According to him the physico-chemical influence of the soil (under the tropical sun) is adverse to the pathogenesis of these diseases is tellural

Diseases which do not thrive in India The list of European diseases affected tellurally in India is a long one The chief amongst them which have attracted attention are — (1) Venereal diseases They do not play the same havoc with the human body in India as in Europe The incidence of parenchymatous syphilis in India is negligible GPI is

a rarity against 500 to 700 cases treated yearly since 1927 in England Tabes is equally rare Other manifestations of syphilis are mild and yield to simple medication True WR positive rate for large towns like Calcutta is under 5.3 per cent and in the country must be considerably lower Gonorrhœa is also mild and does not lead to strictures crippling impotence and sterility to the same extent as in Europe. (2) Disseminated sclerosis This is one of the commonest organic affections of the nervous system in England In India a typical case again is a rarity (3) Infantile paralysis Acute cases seldom attract attention Badly crippled subjects are seen but rarely Atrophy in small groups of muscles is detected occasionally in examining recruits for the army Iron lungs obtained free by some hospitals in India have been used mostly for cases of opium poisoning (4) Encephalitis lethargica [illegible] *Jhinjhinia* of Bengal of 1936 (probably an epider[illegible] damage behind. (5) Other encephalitis of infe[illegible]re almost unknown (6) Streptococcal infection [illegible] o rare Subacute infective endocarditis is seen [illegible]ures until the patient recovers (7) Leukæmias. Cases are few and far between Those of the splenomedullary type keep on reporting for examination for years Some go to Europe for treatment and die within a few months (8) Kidney disease Sufferers passing almost pure water not only live but earn their livelihood (9) Diabetes Even before the days of insulin Indians retired from Government services because of sugar in the urine and even neuritis lived in extra comfort for many years by finding other employments and adding salaries to their pensions (10) Kidney disease

Nervous diseases

Other diseases

Recently the unsuccessful search for cases of erythroblastosis foetalis in the maternity hospitals of Calcutta (civil population of the order of 3 millions so far only one presumptive case reported in this issue has been found) has revealed that even the Rh incompatibility does not operate on Indian soil although the Rh population exists

5. Tropical Neurasthenia

The term neurasthenia has been defined in various ways by different neurologists and psychiatrists This condition is considered by some to be a pathological weakness without discoverable lesion manifested by rapid and great fatigue, physical or mental, or sometimes both It is characterised by functional exhaustion of the tissues especially those of the nervous system due to excessive or undue waste of nervous energy, psychic or motor, and in some cases to acute intoxication The condition, no doubt, is essentially one of emotional unbalance with loss of mental stability associated with undue irritability to external impulses Neurasthenics always experience a sense of fatigue or muscular weakness and complain of being unable to do mental labour, the least concentration being followed by vertigo, headache, etc

Meaning of term

This *readiness* of fatigue is said to be the primary and fundamental symptom of neurasthenia. Beard in his treatise on 'The Nature and D[illegible]

Neurasthen[illegible]

[illegible] its weakened organism even slight tasks a vicious circle of pathogenic activity is formed which encourages a further waste of energy

Left to itself neurasthenia tends to persist unless its cause is removed Under proper prophylactic measures and judicious treatment the prognosis is favourable especially in the cases where organic changes have not had time to undermine the functions of the organs secondarily involved.

(1) Aetiology and Incidence in the Tropics

From a study of the causes of neurasthenia the condition has been well classified as

I Primary or independent of any discoverable exciting causes this has been termed *congenital or prenatal* *Heredity* acts *only* as a predisposing influence through parental neurosis or psychoses No gross visceral damage nor any evidence of serious illness or infection is met with in this type The signs and symptoms are chronic in nature or a recurrent one A careful history will reveal that the individual belongs to a stock of similar victims and this is essentially one of a familial nature This type of neurasthenia is very common in the tropics and mostly met with among children in the same family They manifest it more and more with age at a period of life during which great exertion and anxiety combine to increase the wear and tear of the central nervous system and *indirectly of the organism at large* *Climatic* influence in the tropics and the faulty up bringing of children in such families account for the development of such a state of mind and brain in them They can carry on the ordinary routine of life but any slight deviation from it will surely throw them out of gear resulting in signs and symptoms of nervous exhaustion The picture may be well drawn of such a neurasthenic as suffering from various bodily pains (paræsthesias), abnormal sensations of the brain heart and stomach (hypochondria) The appetite is capricious ravenous one day and bad the next day In short the whole condition is one of irritable weakness with hypochondrial trend.'

The underlying psychopathology of these primary neurasthenics is that the cell units and the neurokyme in them are not sufficiently strong to keep in check and in store the *potential energy responsible for the normal body functions* *A continuous drainage of such* energy demanded by an increased body activity with which the inherently defective neurones cannot successfully keep pace throws the whole system out of balance resulting in a condition of neurasthenia

II The second group constitutes a larger number of ætiological factors and they all come under the type of secondary neurasthenia secondary to some primary causes such as physical ill health with lowered vitality condition of life incompatible with environment, overwork emotional stress It is rightly said that it is not the work but the worry that kills Sudden physical and mental shock continued conditions of fear as seen in maniacs when they are not actually suffering from any disease sometimes predispose to an attack of neurasthenia

Besides the factors mentioned there are others met with People in the tropics live *in a climate in which humidity is added to heat and this will act as a primary causative* factor There are diseases also which are peculiar to the tropics and are seldom seen elsewhere All these affect the daily lives of the people in a way different to the people of temperate zones The maladies and the physical agents such as extreme changes of weather occurring in tropical countries are responsible for the chronic ill health of people and should be considered as factors bringing about a series of signs and symptoms constituting the so called condition of neurasthenia Such causes may be conveniently classified as (*a*) exciting (*b*) predisposing and (*c*) general endocrine dysfunction

[illegible] after-effects of acute fevers in the tropics exposure [illegible] ly selected food etc., are potent factors of [illegible] its after acute maladies either promptly re [illegible] chronic ill health for a long time with sym [illegible] enteric fevers dysentery cholera, intestinal [illegible] the gastro intestinal functions The continu [illegible] the resistance of the organism as a living entity (not only of the nervous system) undermines the metabolic dynamism and *prepares* the soil for neurasthenia.

[illegible]

hæmorrhage or suppurative process, may also be important factors in [illegible] neuroses

Of all the causes those connected with *the male sexual organs have been* credited with the most active ætiological role such as prostatitis posterior urethritis seminal vesiculitis etc, and general disorders and habits such as gonorrhœa syphilis and masturbation.

(*b*) *Predisposing factors* A continued high atmospheric temperature with excess of humidity makes people in the tropics ease loving and much less hardy than those of the

temperate cl mes A little superadded phys cal or mental strain often brings about a ner vous breakdown and makes a man physically unfit to cope with his environment People working in the open spaces get easily tired owing to heat of the sun and cases are on record where many a people after long continued illnesses as malaria kala azar etc., and apparently healthy have succumbed to heatstroke

Due to cl mat c influence in the trop cs and to keep body temperature below the surround ings a large quantity of blood is regularly requ red to flow in the peripheral circulation especially in hot weather People lose appetite in the hot weather metabol sm and ordinary physiological functions and biological processes are depressed lowering body vital ty and making them an easy prey to nerve exhaustion Again in hot weather people are prone

The social conditions of people living in the tropical countries contribute a great deal to the causation of symptoms of neurasthenia —

Contributing factors in Tropics

(1) *Heredity* It accounts for a good number of cases This has already been dealt w th in discussing primary or congenital neurasthenia Women are more prone to this type If as maintained by sexolog sts marriage is an important factor to prevent neurasthenic symptoms in grown up unmarried girls defin te cases are on record where married multi parous women suffer from neurasthenia without any other obvious discoverable causes Other social condit ons as early marriage early and repeated pregnancies associated with ill-nutrition and stra n and stress of life and other maladies make people of the tropics frequent subjects of neurasthenia

(2) *Diet* People in tropical cl mates live on a d et wh ch can be hardly borne by those of temperate countries and so it is held by authorities of publ c health that such a quality of diet cooked
cyanate etc is respon
ulcers etc The d ges
t on and gastralgia is
and gastroptosis is no
colicky pains due to defective intestinal digestion and the resulting fermentation are pro minent features of the later stage In these cases, auto-intoxication is an important feature

(3) *Exercise* That diet and exercise should go hand in hand is an old adage Fat and forty year old Ind ans are often d abetics Visceroptosis and cases of prolapse uteri in quite young Indian girls are the result of lack of proper exercise and such girls always suffer from vague symptoms of neurasthen a such as indigestion attacks of abdominal pain (hypochondria) associated with various endocrine dysfunct ons and particularly of the thyroid and adrenals All these predisposing causes combined with toxins of acute and chronic illnesses characterist c of the tropics play an important role in the causation of neurasthenia

(c) *General endocrine dysfunction* The endocrine system may be thrown out of order as a result of the patient suffering from some acute d sease such as enteric fever cholera bacillary dysentery small pox etc Long continued illness such as malaria kala azar chronic genito urinary d seases or absorption of the toxins arising from putrefactive

must necessarily impair the general dynamism and lower the vascular tens on the underly

associated with low blood pressure

Diagnosis

There is pract cally always in true neurasthen a a long prodromal period, the pre-neurasthenic state characterised by well defined morbid man festations ind cative of aberrant fun
of
dev
sym

of stimulants drugs or tobacco as being symptomatic of organic diseases Neurasthenia should be clearly differentiated from obsessions hysteria, melancholia and hypochondriasis The heart and blood vessels are usually the first to reflect the central functional disturbance *in neurasthenia*

Reviewing the innumerable factors responsible for bringing about the condition of neurasthenia there is no doubt that it is a malady not without obvious causes A proper *diagnosis should be made largely by a process of exclusion All* possible gross organic diseases are to be excluded and careful investigation is most essential regarding the daily life of the neurasthenic together with co
procedure is not adopted several disease
as *neurasthenia Amongst them early*
ill being in an apparently healthy your
sclerosis, cerebral tumour cerebral ar
paralysis of the insane and dementia præcox deserve special mention

A line of demarcation should be drawn between real organic diseases and the functional disorders of the nervous system Besides the diseases mentioned which simulate symptoms of neurasthenia there are many more which cannot be discussed here for want of space

(2) Treatment

The prognosis and the line of treatment depend chiefly on a right diagnosis *of the cause of neurasthenia Cases of secondary neurasthenia always make* a complete recovery after removal of the primary causes and all that is needed is proper rest and treatment of those diseases There may occur periods of improvement but relapses occur readily

The treatment of cases of neurasthenia does not merely consist in the application of specific drugs against such diseases as are responsible for its development Although the importance of such a procedure should always be recognised, general tonics such as phosphorus (glycerophosphate of iron, both organic and inorganic), arsenic (with all its synthetic preparations) and *strychnine combined with nourishing and proper dieting, regular and* graduated exercise and open air life, rest mental and physical, distraction and removal of baneful influences as far as possible constitute the prominent features of the treatment

The benefits of rest in the average case may be secured by spending four to six additional hours in bed, by retiring early and getting up late Or, if it *is convenient, a couple of hours rest during the day may replace the morning*
hours of
regulated t
changes of

Isolation is beneficial when neurasthenia is accompanied by very marked symptoms of lowered nutrition and muscular weakness and when a prolonged rest in bed is insufficient to arrest emaciation. Over feeding is sometimes *obligatory and may be carried out* by the addition of milk and eggs to an ordinary mixed diet between meals

Gastric functions should be analysed and diet adjusted accordingly along with administration of dilute hydrochloric acid before meals where hypo or anacidity is found Any foci of infection present should be properly dealt with

Women mostly suffer with a train of abdominal symptoms due to lack of tone of involuntary muscles of the various abdominal organs and such diseases are cœcal stasis, prolapse of abdominal viscera and various other pelvic organic diseases Patients with visceroptosis are very commonly met with complaining of vague abdominal pains A skiagram always *settles the diagnosis* The patient should be advised proper abdominal exercises, small but frequent dieting a well fitting abdominal belt and sometimes electrial treatment with sinusoidal

current. Cases are on record which show that this line of treatment has cured many such neurasthenic patients Chronic cœcal stasis should be treated by regular abdominal massage and by drugs such as cascara, senna leaves or pods stewed with prunes, etc Sometimes surgical measures are adopted to cure patients with neurasthenia Removal of the appendix, fixation of the floating kidney, gastropexy and a few pelvic operations in females have been known to cure neurasthenic patients

In cases of neurasthenia resulting from sexual abuse, rest of function is essential Local treatment, especially of the verumontanum has been widely advocated, but some believe that such treatment only acts by suggestion. Sexual neurasthenia is often ascribed to a definite pathological condition of the genito urinary tract especially in the vicinity of the verumontanum but some authorities do not agree on the point Electricity has been advocated by many Static electricity, slowly interrupted faradic current or diathermy may be conveniently employed

Hydrotherapy has also been highly recommended Winternitz's method of cold pack along with the application of warmth (122°F or 50°C) over the epigastrium or the application of cold over the spine is credited with marked efficacy Sleep is favoured by taking a warm bath for ten minutes followed by a glass of hot milk just before retiring

Medicines Few medicines are of value, the elaborate process of nutritional repair, favoured by the aid of the above mentioned procedures, renders drugs relatively unnecessary

Drugs

Neurasthenia is recognised to be a vasomotor neurosis, the prominent feature of which is relaxation of all arteries due to exhaustion of the sympathetic centre and the resulting loss of propulsive power of the arterioles The tissues thus become imperfectly oxygenated and nourished, hence mental torpor, habitual fatigue, adynamia and gastro intestinal atony result There are various functional disturbances associated but certain degree of hypothyroidism is always present Hence small doses of desiccated thyroid is recommended by some usually in combination with strychnine and full amounts of an assimilable form of iron such as Blaud's pill Strychnine is supposed to be almost a specific in neurasthenia Doses should be gradually increased and excess of 6 mg (1/10 gr,) may be given in daily doses Arsenic, iron and other tonics are often valuable Of the [illegible] which equals [illegible] ery efficient [illegible]

Laxatives are important to counteract the auto intoxication The intestine should be flushed with calomel and a saline purgative at the start Later, cascara, rhubarb, or aloin are suitable The endless complaints and fault finding nature of neurasthenics are in most cases symptomatic Psychotherapy is usually effective in such cases Sympathy and consideration on the part of the attending physicians, always gain the patient's confidence and ensure his co-operation which is of primary importance in the curative measures instituted

Under proper prophylactic measures and judicious treatment however, prognosis is usually favourable The just merit of each individual case should be taken as the guide to treatment

CHAPTER XII

METABOLIC DISEASES

DIABETES MELLITUS AETIOLOGY AND CLINICAL ASPECTS, TREATMENT DIETETIC, INSULIN—HYPOGLYCAEMIA AND DIABETIC COMA—OBESITY AETIOLOGY AND CLINICAL ASPECTS TREATMENT—INFANTILE BILIARY CIRRHOSIS—GOUT

DIABETES MELLITUS

Diabetes mellitus is a disorder of metabolism, characterised by polyuria, excessive thirst, hyperglycaemia and glycosuria, and a progressive loss of weight.

Diabetes is a disease which should prove to be of great interest to any one working in India not only because it is extremely common here more particularly in Bengal but also because the disease was known to the ancient Hindu writers as early as the 6th century B C Charaka (2nd century A D), the most renowned Hindu physician of his time described some of the cardinal symptoms of diabetes (including the presence of sugar in the urine) in his Charaka Samh
from a much earlier work of Agnivesa
of his master Atreya (6th century B C.
home in the tro
of this country
diabetes are to
means to pour
writers Thoma
sweet taste of diabetic urines in 1670
between diabetes mellitus and diabetes

1. Aetiology and Clinical Aspects

In 1889 Von Mehring and Minowski produced diabetes mellitus experimentally in dogs by extirpation of the pancreas Later Opie showed that the pathology of the disease was centered in the islets of Langerhans, and in 1922 Banting and Best succeeded in *preparing insulin from the islet tissue of glands in which ligation of the pancreatic duct* had produced degeneration of the acini Signs of chronic hyperinsulinism have been observed in a number of cases in the presence of adenomata of the islet cells

The consensus of the present day opinion is that a pancreatic lesion plays the most important part in the aetiology of diabetes and that the root cause of diabetes centres round the islands of Langerhans though the nature of the factor or factors giving rise to the diseased condition of the islet cells has not yet been clearly understood *The predisposing causes which directly or indirectly are likely to throw undue strain on the islet cells of the pancreas and cause their hyaline degeneration and atrophy sooner* or later
sedentary habits lack of physical exercise,
ons etc. Heredity is also believed
of cases diabetes could be traced

Climate is also believed by many to be one of the factors It has been stated that tropical and sub tropical climates lower the carbohydrate tolerance of individuals Basset Smith has observed that under the influence of the tropical heat there is a tendency to *the retention of carbonic acid in the alveolar air in people at rest* and also to the production of glycosuria and acidosis particularly in the well fed

Coming to the incidence of diabetes among the different races of India the writer is of opinion that Bengalee Hindus appear to be more prone to diabetes than any of the other races *the proportion being 68 per cent among the total cases*

Infections of any kind may prove to be a direct cause of diabetes probably owing to some kind of damaging effect on the pancreas by the toxin Lawrence and Buckley have proved by experiments that diphtheria toxin will practically annihilate the action of insulin

The commonest lesion found in diabetes mellitus is a hydropic degeneration and vacuolation of the beta cells of the islets of Langerhans These changes are however absent

in many cases particularly in children in whom it has been suggested that the cause is a congenital reduction in insulin forming tissue, rather than the result of a pathological process

Symptoms

Clinically two principal forms of diabetes are recognised, acute and chronic The acute form is generally found among young people and usually runs a rapid course Mild chronic forms of the disease are usually common in middle aged persons but such cases may gradually develop into the severer form and then the disease runs the usual rapid course.

Mild cases may be entirely without symptoms, or these may be confined to a mild degree of polyuria or a feeling of fatigue at the end of the day This type is most frequently encountered among elderly people who are often obese and have arteriosclerosis In severer cases, thirst, polyuria, excessive fatigue and loss of weight are usually present Pruritis is common, especially amongst women Visual disturbances are frequently complained of, and cataract may develop Excessive hunger is often met with in young diabetics

A condition of mild neuritis is often met with and causes pains in the legs, diminished vibration sense, and loss of ankle-jerks Severe neuritis is uncommon

Diagnosis

The diagnosis of true diabetes mellitus is often an easy matter when the patient presents the usual signs and symptoms, but there are many cases in which considerable difficulty is experienced and elaborate laboratory methods of diagnosis are necessary

The average normal fasting level of blood sugar in man is 0 1 per cent After a meal consisting of carbohydrates the blood sugar rises reaching a maximum level of 0 17 per cent within one hour and coming down to the normal level again, usually within 1½ to 2 hours The reason why it comes back to the normal level is because a part of the extra sugar is changed into glycogen and stored as such in the liver and part of it undergoes combustion in the muscle tissues In the diseased condition, the picture is quite different for owing to the inability of the diabetic individual to store sugar as glycogen or burn it like a normal person, the circulating blood of the diabetics contains excess of glucose Thus in mild cases the fasting level is usually found to be 0 13 per cent or over In more severe cases, it is of course proportionately higher, according to varying degrees of defect in the storage mechanism

In many cases of potential diabetes and even in cases of mild diabetes, however, the fasting level of blood sugar may be perfectly normal and the urine may be aglycosuric even after meals owing to a varying leak point In such doubtful cases, the glucose tolerance test should be done and the behaviour of the blood sugar after a glucose meal should be investigated A healthy normal person should conform to the following —

(1) The fasting blood sugar level should be normal

(2) The maximum rise of blood sugar after ingestion of 50 gm of glucose should take place within one hour and should not go beyond 0 17 per cent

(3) The drop of the blood sugar to the normal level should take place within 1½ hours after the glucose is taken

(4) No glycosuria should occur

A diabetic blood sugar curve after a glucose meal deviates from the above according to the varying degree of defect in the storage mechanism, judged according to the rise of the initial (fasting) level of blood sugar, a tendency to a much heightened curve and a much delayed return to the normal level

2 Treatment

The fundamental principle underlying the successful treatment of diabetes is based on the knowledge that a careful adjustment of the diet with or without the use of insulin as an adjunct will prevent hyperglycaemia and hence eliminate glycosuria and thus will tend to give rest to the already overworked and diseased islet cells of the pancreas There is plenty of evidence in the literature to *prove that if hyperglycaemia can thus be prevented* the progress of the disease will be arrested gradually the distressing symptoms of the disease will disappear and in the majority of cases the tolerance of the patient will improve considerably

Thus it appears that the treatment of diabetes mellitus falls mainly into two main groups —

(1) Dietetic treatment This means that the patient should be given only that amount of food which is absolutely necessary to meet the minimum metabolic requirements of the body This is known as the basal diet

(2) Insulin treatment It should be remembered that insulin treatment is only a valuable adjunct to the dietetic treatment for which it can in no sense be considered to be a *substitute* The indication for insulin treatment will be considered later on

(1) Dietetic Treatment

In calculating a basal diet for diabetic patients the following points should be considered —

(1) The caloric value of the diet should not be less than 25 calories per kilo of the patients body weight

(2) The protein content of the diet for an young adult should be about 1·4 gramme per kilo of the body weight

(3) The fat content of the diet should be fairly low

Bose s formula for calculating the basal diabetic diet is given below —

Total caloric requirement of the patient = weight of the patient in kilo × 25

$$\text{Protein requirement in grammes} = \frac{\textit{Total caloric requirement}}{20}$$

$$\text{Carbohydrate requirement in grammes} = \frac{\text{Total caloric requirement}}{16}$$

$$\text{Fat requirement in grammes} = \frac{\text{Total caloric requirement}}{16}$$

Thus a diabetic individual weighing 64 kilo (10 stones) will require the following diet —

Total caloric requirement = 64×25 = 1 600 calories

$$\text{Protein requirement} = \frac{1600}{20} = 80 \text{ grammes}$$

$$\text{Carbohydrate requirement} = \frac{1600}{16} = 100$$

$$\text{Fat requirement} = \frac{1600}{16} = 100$$

The number of grammes of carbohydrate protein and fat and the caloric

value of the diet required being thus ascertained the patient s diet is framed by the use of food tables

For ready reference a sample diet chart (suitable for a diabetic patient weighing 64 kilo as mentioned above) having the above proportions of food principles is appended below —

Bread	5	oz
Butter	1	oz
Eggs	2	only
Fish or chicken	4	oz
Mutton	6	oz
Green vegetables	16	oz
Milk	8	oz
Ghee	1½	oz

Approximately Carbohydrate=100 gm Protein=80 gm Fat=100 gm Calories=1600

On a diet calculated as above the average diabetic patient of the mild type usually becomes sugar free in about four days and the blood sugar comes down to the normal level in about a week s time If however the patient does not become sugar free or does not maintain the blood sugar at the normal level on the above diet insulin treatment is usually indicated

(2) Insulin Treatment

As mentioned before insulin treatment in cases of diabetes should be cons dered as a valuable adjunct to the dietetic treatment in order to get the full benefit of the insulin and the quantity of diet allowed It should also be kept in mind that unlike most drugs insulin has no fixed dosage and that no hard and fast rule can be laid down regarding the dosage of insulin inasmuch as it may vary in individual cases according to the severity of the case complications the diet prescribed and various other factors

Insulin

Another important factor which should be considered is that the amount of glucose utilised per un t of insulin varies in different cases It has however been roughly estimated that one unit of insulin usually causes 1 to 2 gm of carbo hydrates to be utilised in a moderately severe case of diabetes In a milder case

the carbohydrate tolerance of the patient and the amount of glucose which is over the limit of tolerance *i e* the total amount excreted in the urine must be covered by an adequate dose of insulin calculated in the way mentioned above

Hints on insulin treatment

1 There are no hard fast rules regarding the dosage of insulin in a parti cular case as it varies with the complications and the amount of fasting hypergly cæmia It is always best to begin with a small preliminary dose

2 Insul n is certainly indicated in all cases of severe diabetes mellitus with pronounced hyperglycæmia and marked glycosuria with or without ketosis

3 Insulin is also indicated in the milder forms of the disease where a careful d etetic regime has failed to remove glycosuria or reduce the fasting hypergly cæmia say below 0 15 per cent

4 It is always best to give insulin injection 20 minutes to half an hour before meals

5 All forms of hard or strenuous exercises should be forbidden for at least 3 to 4 hours after insulin injection

6 Roughly speaking it may be assumed that one unit of insulin causes 1 to 2 gm of carbohydrates to be utilised in a moderately severe case of diabetes In milder cases the carbohydrate utilisation per unit of insulin is greater

Early symptoms (1) Unaccountable nervousness The patient feels some impending danger (2) Listlessness (3) Tremulousness or actual tremors particularly of the extremeties (4) Dim vision sometimes diplopia (5) Great desire for food—a sinking feeling in the pit of the stomach (6) Vasomotor disturbances—pallor of the face alternating with flushing and sweating (7) Palpitation of the heart

Late symptoms (8) Mental confusion—low muttering delirium (9) Loss of deep reflexes (10) Muscular twitchings and convulsions (11) Coma

Treatment The treatment is simple if undertaken early The patient should be put to bed A tablespoonful of glucose powder dissolved in water and given by the mouth is the best but if it is not at hand ordinary table sugar will form quite a good substitute Orange juice 4 to 8 oz may also be given if available If the symptoms persist after ¼ hour more sugar should be taken If the milder symptoms are overlooked or not given heed to and they are allowed to pass on to the coma stage ½ to 1 ccm of solution adrenaline chloride (1 in 1 000) should be given intramuscularly Glucose may be given intravenously if necessary

8 Hypoglycaemia and Diabetic Coma

A diabetic patient may become comatose because he has either too little or too much insulin Two kinds of coma are generally recognised and the signs and symptoms following one should be distinguished from the other

In insulin (or hypoglycæmic) coma the normal colour of the skin is generally preserved or it may be very white The respirations are shallow but the breath does not smell of acetone The urine is usually sugar free and does not contain aceto acetic acid but may contain both if the bladder has not been emptied for some hours The blood sugar is below 0 07 per cent or may be as low as 0 04 per cent In diabetic coma on the other hand the symptoms are fortunately quite characteristic The skin is usually flushed the respirations are deep and the breath smells of acetone The urine always contains large amounts of sugar as well as acetoacetic acid and the blood sugar is over 0 2 per cent and may b even as high as 0 5 to 0 8 per cent In hyperglycæmic condition if the patient is not deeply comatosed the initial dose should be 50 units but if coma be deep 70 or over 100 units of insulin should be injected at a time But if the patient is used to large doses of insulin the initial dose should be at least half as great as the doses recommended for ordinary cases Administration of sugar is always desirable along with the injection of insulin to avoid hypoglycaemic coma In cases of deep coma 600 ccm of a 2 [illegible] should be given with 50 gm of glucose [illegible] estimation of blood sugar where [illegible] for sugar every three hours should always be done to note improvement of the patient A repetition of treatment may be necessary where improvement is slight or even absent [illegible] hours after the first one If [illegible] be given if no impro

should be repeated, and if the patient is worse the dose should be half as much again

The risk of precipitating a hypoglycæmic coma should always be borne in mind while carrying on insulin treatment for diabetic coma The most usual signs in such cases is a relapse into deep coma after a partial recovery of consciousness This emergent condition demands prompt treatment One ccm (ten units) of pituitrin or one ccm of adrenalin should at once be injected and this is to be followed by an intravenous injection of 300 ccm of 20 per cent glucose solution The treatment raises the blood sugar and the patient regains consciousness In the following lines a general outline of treatment is given

1 Put the patient in bed in charge of a trained nurse Keep him warm with blankets and hot water bottles if necessary If there are indications of circulatory collapse give digitalin caffeine camphor or other suitable drugs

2 Evacuate the large bowel by an enema If there is much vomiting gastric lavage should be done

3 Give insulin as soon as possible No hard and fast rule can however be laid down regarding the initial and the subsequent dosage of insulin and the mode of its administration in as much as it depends on the depth of the coma the general conditions of the patient the blood sugar level and various other factors As a general rule it may be said that in a case of moderate severity [illegible]
initial d[illegible]
intraven[illegible]
by mout[illegible]
unconscious

4 In severe cases where there is severe dehydration due to loss of fluid and collapse prompt treatment is essential to save the patient from death and the case is to be treated on similar lines as in cholera Introduction of saline intravenously subcutaneously and rectally should be done as early as possible It is best to combine 10 per cent glucose with normal saline One pint of this solution will contain 60 gm of glucose and should be given very slowly by the intravenous route immediately after the insulin injection The injection of 0 5 ccm of adrenalin chloride solution (1 in 1 000) in addition sometimes helps in restoring the feeble pulse This may be repeated after 4 hours according to the state of the collapse If the patient s condition improves sufficiently only [illegible]
[illegible] ever have
[illegible] a judged

OBESITY

1 Aetiology and Clinical Aspects

Obesity bases as a disease of fat metabolism and is characterized by super fluous deposits of fat in the body

To define obesity as a disease of overnutrition would however be more correct In healthy man the need of food is undeniably registered as hunger and the filling of the need by disappearance of appetite and a feeling of satiety This regulatory principle suffers under abnormal nutritional circumstances We learned this fact in Germany in the years following the First World War Foodstuffs which the Germans had to deny themselves for years were available again in increasing amounts The mechanism which had been practically out of use for so long no longer functioned accurately There followed a

Aetiology

The underlying principle is to give a diet of caloric value below that required for the optimum weight of the patient As a general rule it should be 20 to 25 per cent below his normal requirement Great care should at the same time be taken in preserving the proper nitrogen equilibrium of the patient which is of great importance The diet should be arranged in such a way that the patient is forced to burn his own fat without the loss of his body proteins This is not difficult to accomplish provided the diet contains sufficient proteins and is of a low caloric value Usually, 1 5 gm of proteins per kilo of the body weight will answer the purpose It should also be remembered that carbohydrates in the food besides being the chief source of energy for the maintenance of the body temperature and for the production of work, are most efficient protein sparers and every use should be made of them to preserve the nitrogen balance at an economic level At least 50 per cent of the energy contained in the food should come from the carbohydrates Thus in calculating a reduction diet the caloric value of the protein allowance should be calculated first and to this should be added an amount of carbohydrate sufficient to bring the caloric value up to the desired total caloric intake Fats need not form an item of any importance in the dietary of obese persons

According to Browning (1934) the essential factors in the choice of a dietary are —

(1) *Preservation of nitrogen balance* To do this the proportion of protein to carbohydrate should be about 1 gm of protein to 0 6 gm of carbohydrate with a total of not less than 60 gm of protein

(2) *Minimum fat intake* As already stated fat is cut down from the dietary so that the patient is forced to burn his body fat to supply the metabolic need

(3) *Avoidance of hunger* This can be avoided by giving high proportion of fruits and vegetables which have low caloric value

(4) *Maintenance of water balance* Sometimes the patient shows a tendency to store water in the tissue though he may be losing a good deal of fat This is prevented by giving a salt free diet and increased quantity of protein

(5) *Adequate mineral and vitamin content* The loss of mineral content with the use of the recommended diets is not great If the fat is very much restricted there is likelihood of the vitamins A and D being reduced below the standard level This can be remedied by giving carotene and irradiated ergosterol A cup of yeast extract once a day will supply vitamin B

(6) *Physiological factor* It is in many cases difficult to induce a patient to change to a diet of small quantity and simple character Under these circumstances a slow reduction is preferable to a drastic one, the foods should be distributed over the various meals allowed to make them as palatable as possible.

A very efficacious diet (modified by Douthwaite 1934 from Williams) is given as follows

On waking A glass of water *Breakfast* Tea or coffee sweetened with saccharine, one slice of dry toast no butter, 3 oz of cold tongue boiled sole haddock or whiting, fresh fruit *1 p m* A tumbler of water *Lunch* 4 oz of chicken or meat (except pork), but no gravy vegetables as given below cooked without fat, salad without oil, one square of vita weat, fresh fruit *5 p m* Tea without milk or sugar *Dinner* Bouillon fish, 2 to 3 oz of game or meat (except pork) no bread sauce or bread crumbs vegetables as mentioned below, salads, one slice of toast dry wine fresh fruits coffee with

saccharine, condiments are allowed Worcester and anchovy sauces, ketchup pepper, mustard vinegar, walnut pickle horse radish salt sparingly

Vegetables allowed Green vegetables (except peas), celery, seakale asparagus and salsify

Another form of dietary has been devised by Evans and Strang (1929), one gramme of protein per kilo body weight is given along with some carbohydrate to maintain nitrogen equilibrium

Evans and Strang Diet (about 650 calories), *Breakfast* One egg and 1 oz of bread *Lunch* One egg and 4 oz of vegetables as below *Dinner* One cup of bouillon and 3 oz of lean meat, 4 oz of vegetables Vegetables allowed Lettuce, cucumber, spinach, asparagus endive, celery, mushrooms tomatoes, sprouts, watercress, cauliflower, radish, cabbage

Water as much as needed, no fried foods, a teaspoonful of bicarbonate of soda daily

It is essential to eat the whole amount mentioned in this diet A modification of this diet is given by Dodds (1934) which allows only 8 calories per kilo Though efficacious it is rather drastic There is a tendency to acidosis with Evans and Strang diet, which may be relieved by the use of sodium bicarbonate

Kenyon's modification (1933) is to give 1,000 calories which allows high protein, vitamin and mineral salt

Breakfast One portion of fruit one egg and white of one egg, coffee, tea bread substitute (for example, Heudebert's breadsticks) *Lunch* 3 oz lean meat fish, or fowl, ½ pint 5 per cent vegetables, one portion fruit Tea *Dinner* 3 oz meat, fish, or fowl and vegetables as at lunch 9 30 p m Half cup orange juice, 1 oz bemax In addition, 1½ glasses skimmed milk daily (for calcium content), one capsule haliverol t i d (for vitamin content)

A fruit portion—one orange, half a grape fruit, one medium apple, two medium peaches, one small pear, one cup strawberries, one cup blackberries

It is important to control the body weight by weekly measurements When the desired weight has been obtained, the diet is slowly increased

Exercise

The therapeutic factor next in importance to the restriction of food is the stimulation of the metabolism by physical exercise Exercise hastens the metabolic rate and leads to increased oxidation of the ingested food, or if sufficient food is not available, of the body fat The exercise should be gradual and regular and should not be carried up to the point of exhaustion

The other factor which also serves as a useful physical stimulus to metabolism is a cold shower or plunge bath and should be advocated where there are no contra indications for it such as, severe myocardial degeneration arteriosclerosis and high blood pressure

Endocrine therapy

As it is possible to control obesity with dietetic restrictions in many cases, endocrine therapy should not be indiscriminately resorted to Thyroid has been too frequently used to stimulate metabolism and reduce weight In those cases where the basal metabolic rate is below normal, the patient will probably lose weight after thyroid medication Unless properly controlled, even in cases of myxœdema the weight after an initial fall may be increased after administration of thyroid In thyrogenous obesity and other forms where metabolic stimulation is required thyroid should be used in doses of half a grain twice daily, this is gradually increased to 1 gr three times a day Some cases may require much larger doses Other endocrine preparations such as pituitary, or combination of

thyroid and pituitary, or treatment by extracts of genital glands have been advocated, but the effect of such therapy after oral administration seems to be uncertain

It has been shown that certain nitrophenols are capable of causing a marked increase in both the temperature and oxygen consumption Cutting and his co-workers (1933) found that by using a drug of this nature, which is 2 4 dinitrophenol, the metabolic rate of animals could be raised by 50 per cent by a dose of 10 mgm per kilo body weight In human beings the drug in doses of 3 to 5 mgm per kilo body weight daily raised the metabolic rate by 40 per cent and this was accompanied by an average loss of weight of 2 lb a week As this compound has been known to be toxic, Dodds and Pope (1933) working with dinitro o-cresol (dekrysil) found that it would produce the same effect in much smaller doses of 1 mgm per kilo daily Douthwaite (1934) has used this drug in doses of 1 mgm per kilo thrice daily, and later once daily, though the constitutional effects were not marked with smaller doses, the loss of weight was very insignificant These drugs are in the experimental stage and should, therefore, be used with caution

In addition to these measures, other methods of therapy have a great bearing on the final success in treatment Excretion of waste products of metabolism should always be favoured, and with this end in view the activities of bowels kidneys, skin and lungs should be watched

INFANTILE BILIARY CIRRHOSIS

The aetiology of disease is unknown but it is common in cities than in villages and is liable to run in families Toxins in the maternal diet during pregnancy, dietetic errors in the mother and child, excess of fatty and farinaceous food and mineral or vitamin deficiencies, have all been suggested as causal factors In some children of a family the disease has been averted by sending them to a better climate and surroundings different from those in which the previous children contracted the disease This may suggest that a climatic and environmental factor is involved

In the early stages of the disease the liver is greatly enlarged. The enlargement is uniform and the surface smooth Ascites is usually present, and the gall bladder is shrunken

The characteristic histopathological change consists of formation of fibrous tissue, at first primarily within the lobules but later extending to the sheaths and interlobular tracts There is a characteristic multiplication of the bile-ducts which appears to be connected with the destruction of liver cells In advanced cases there is great destruction of liver tissue and in some areas the whole field may appear to consist of fibrous tissue and scattered masses of granular debris

In the early stages of the disease jaundice is slight and is due to destruction of the liver parenchyma The van den Bergh reaction is usually indirect biphasic and delayed Later the jaundice becomes more intense and is due to biliary obstruction the serum giving a direct van den Bergh reaction

Early symptoms are vague and the disease is not generally suspected unless there is an indicative family history Enlargement of the liver is noted at an early age and may attract the parent s attention The liver is uniformly enlarged not tender at first, but becomes slightly tender as jaundice develops Usually the left lobe enlarges at first and may reach down to the spleen The c ... gradually fills the abdomen Flatulence is marked ... able with loss of appetite, fever, and prono ... only enlarged, but never to the same extent as ... ttent or low remittent type is usual

In the early stages the stools may lose their normal colour and as the disease

progresses they become white or clay coloured and often offensive The urine is scanty and deeply bile stained

In the terminal stages there may be generalised anasarca and the liver may contract In some cases fatal hæmorrhages may occur from the bowels or stomach

The disease usually runs a chronic course of from six to eighteen months The prognosis in advanced stages is bad, and the majority of cases prove fatal inspite of treatment In the earlier stages the outlook is uncertain Most cases in whom the liver is hard, tend to get worse and die Generally speaking the harder the liver, the worse the prognosis

Treatment

In the early stages, a change of diet and climate gives perhaps the best chance of cure Treatment is unsatisfactory and should be directed to relief of the early gastro intestinal symptoms and to improvement of hygienic surroundings The infant should be put on diluted or citrated milk milk whey, or peptonized milk Skimmed milk has also been advocated Fruit juices should

Medicinal treatment is of doubtful value A prescription such as mercury with chalk 1/12 gr, salicin 1 gr, ipecacuanha 1/12 gr, extr euonymus 1/6 gr and sod bicarbonate 2 gr, is usually given two or three times a day Liver extract emetine hexamine, and an indigenous preparation kalmeg have all been tried but with doubtful results

GOUT

Gout is a luxury disease Great stress has been laid on the inherited predisposition to gout and some go so far as to say that gout is always a hereditary disease and that all the other factors are merely determining agents and in themselves incapable of giving rise to gout in the absence of hereditary taint

Gout is an even more remarkable disease than has hitherto been recognised Is it to be supposed that certain races have a special inherited predisposition to gout while others are immune? Before such a view is accepted it must be clearly demonstrated that environment is incapable of accounting for the special frequency of gout in particular peoples

Is it on account of differences of inherited structure that the people of some parts ... so free from the disease? ... d in spite of the extent ... ancestry with the people

It will certainly be difficult to eliminate heredity as a factor in the causation of gout unless it is clearly understood that the environment of the human being does not begin to act after birth it has already produced a most important influence on the unborn babe The child of a mother who has been living in the manner customary among gouty families has been nourished on what may be called gouty blood all through its intrauterine life

That fact is of great importance in connection with the future constitution of the child The alternative seems to be a frank recognition of the inheritance of acquired characters for it is hardly to be admitted that certain groups of people in other respects exactly like each other, have been specially constructed in such a way as to make some of them susceptible to gout, and others insusceptible On the other hand, wherever gout is common, *there certain habits of life are common These habits constitute the environment of the people* and they influence even the unborn children

Gout is not at all common in India but the disease is of considerable importance to workers in India all the same It is becoming more and more recognized in this country A diagnosis of gout is often made in India when it is not at all justified there are excellent examples of the diseases that are so often confused with gout

Typical cases of gout are sometimes seen among the well to do classes in northern India and the writer has personal knowledge of such cases They are hardly ever seen in the out patient departments of hospitals

LATAH

Latah is an unusual form of mental disturbance which is not infrequently

encountered amongst the native populations of the Malay Peninsula the Indonesian and the neighbouring islands It appears more often in women especially at the menopause, and is rare before puberty The condition persists for years but shows no tendency to get worse, and does not progress to insanity *It is not amenable to any form of therapy*

ology Victims of this disease, who have hitherto appeared quite normal may suddenly *in response to some stimulus, such as a loud sound or overt suggestion*, pass into a peculiar hypnotic-like mental state, during which they may involuntarily perform certain movements or utter certain sounds or words Patients in such a trance, which usually lasts only a few minutes may be entirely at the mercy of their prompter, and may follow any lead givenewithout regard *to consequences The trance usually leaves no ill after effects*, though in some severe cases, the patient be left utterly exhausted, or may even faint It is well known amongst the Malays that Latah victims never 'run amok', and are only very rarely involved in criminal acts The disease does not progress and no effective treatment is known

RUNNING AMOK

Running amok is a form of mental derangement, which when fully developed causes its victims to exhibit fits of senseless fury, during which they may run mad and murder innocent people, often without any obvious reason whatsoever The tendency to such derangement *is* greatest amongst the Malays, and the prevalence of the abuse of narcotic drugs such as *Cannabis Indica* are considered as aetiological factors Chronic malaria has in recent years been strongly incriminated as an exciting factor

The victim of this disorder usually nurses some grievance against a particular person *and sullenly broods over it for some time He then suddenly decides* to destroy both that person and himself, and as many other people that come in his path as possible Arming himself with a knife he sallies forth, stabbing any body that he encounters, whether it be friend or supposed enemy

Van Loon in Java reported that he found amok runners frequently suffering from infectious disease malaria has also been incriminated They exhibit symptoms of hallucinations and mental confusion, and are urged to run away *and attack others in reaction to some imaginary danger* and the apprehension and terror it causes

Treatment consists of administering sedatives, and making a search for malaria, or other infective disease, which must then be adequately treated

KORO

Koro, which is well known among the Chinese as '*Shook Jong*' is a condition which occurs among the Macassars and the Bunginese in the Celebes Islands The affected patients, at regular intervals, *get a strong and frightening sensation* that the penis is being pulled up into the abdomen The patient grasps his penis to prevent this happening, and gets others to help him If not helped the patient may die of an acute anxiety state The penis may be tied to the leg with strings and pins by the frantic patient in his efforts to avoid the supposed disaster, and *this state may continue for days* before it subsides It is believed that local pathological conditions such as hernia, hydrocoele, elephantiasis of the scrotum, or œdema of the lower abdomen may be the causes which provoke the actual attack

Treatment consists in administering sedatives and hypnotics, reassuring the patient, and dealing with any *local pathological lesion that may be present*

PART II

REMEDIES USED AGAINST HELMINTHIC DISEASES

HELMINTHIC CONSIDERATIONS—SEROLOGICAL CONSIDERATIONS IMMUNITY DIAGNOSTIC TESTS—TREMATODES OR FLUKES OF MAN GENERAL CONSIDERATIONS TREATMENT WITH ANTIMONY COMPOUNDS TREATMENT WITH EMETINE AND OTHER DRUGS LIVER INTESTINAL AND LUNG FLUKES—TAPE WORMS OF MAN CLASSIFICATION INTESTINAL TAPEWORMS LARVAL TAPEWORMS—NEMATODES OF MAN CLASSIFICATION HOOKWORM ASCARIS TRICHURIS STRONGYLOIDES AND ENTEROBIUS—TISSUE NEMATODES FILARIAE DISTRIBUTION IN INDIA LOA LOA GUINEAWORM ONCHOCERCA TRICHINELLA—GENERAL CONSIDERATIONS OF ANTHELMINTIC DRUGS DRUGS ACTING ON INTESTINAL HELMINTHS DRUGS ACTING ON TISSUE HELMINTHS MODES OF ADMINISTRATION CRITERIA OF CURE EXPERIMENTAL INVESTIGATION—DRUGS USED AGAINST HELMINTHS MALE FERN AND ALLIED DRUGS CARBON DERIVATIVES TETRACHLORETHYLENE CARBON TETRACHLORIDE OTHER CARBON DERIVATIVES THE ESSENTIAL OIL GROUP OIL OF CHENOPODIUM OTHER ESSENTIAL OILS SANTONIN THYMOL AND ALLIED COMPOUNDS THYMOL BETANAPHTHOL RESORCINOL DERIVATIVES HEXYL RESORCINOL HEPTYL RESORCINOL TRIPHENYL METHANE DERIVATIVES GENTIAN VIOLET MISCELLANEOUS ANTHELMINTICS—PRESENT POSITION OF ANTHELMINTIC DRUG THERAPY

1 Helminthological Considerations

(1) Historical and General

General

From time immemorial helminths were known to human beings their effects on hosts human and animal were recognised and attempts were made to eradicate them by various drugs In Egypt (1600 B C) a worm pathogenic in the human body was described The Greeks (490 B C) were aware of infection by tapeworms and roundworms and laid down corresponding lines of treatment Hippocrates diagnosed hydatid disease and suggested a technique for removal of the cysts The Persian physician Avicenna (980-1036 A D) classified the helminths and listed many medicaments for expelling them mentioning also the precautions in each particular form of treatment In the middle ages in Europe a distinct advance in the knowledge in anthelmintics was made Nevertheless it is only lately that the study of anthelmintic drugs has been taken up on scientific lines The modern era of anthelmintic therapy is based on a comprehension of the biological and pathological processes of the parasites and a knowledge of toxicity and specific anthelmintic action of several important drugs Moreover the comparative study of toxicity and specificity of drugs seem to eliminate a few time honoured so called specific drugs from the minds of physicians because of their high toxicity and lack of specificity In their place have been found new drugs with lower toxicity and surer action and in many instances the need for a better chemotherapeutic agent has stimulated the synthesis of superior drugs

The worms which have been recorded as parasites of man and domestic animals are numerous They belong to a number of different divisions or phyla

while others pass either the larval or adult stage in man and the second part in animals Thus we can classify helminths into three groups —

1 Helminths living as adults both in man and animals
2 Helminths passing larval stage in animals and adult stage in man
3 Helminths occuring as adults in animals but as larvae in man

Infection with helminths may only rarely be seen in man whereas it is quite common in animals In these cases animals seem to act as 'Reservoir Host' passing infection to man from time to time Going further into the life history of these parasites and studying the mode of infection of man it is realized that the control of helminthic infections in man is not possible without control of these among animals side by side

Prevention of helminthic infections in animals is however a very difficult problem particularly in India where no care of sanitation or water supply of animals is taken Animals eat un-cooked food soil the food with their own dejecta and drink water from ponds and streams from which they infect themselves

The general methods of prevention and control have been summarized by Leiper as follows —

1 Medication by means of anthelmintics and therapeutic drugs

2 Prevention of the entry of the infective stage by any of the following means —

(*a*) Avoid exposure to infective soil Use of boots recommended
(*b*) Avoid open air bathing in places liable to contamination
(*c*) Avoid use of unfiltered water for domestic purposes
(*d*) Avoid use of uncooked foods
(*e*) Avoid overstocking

3 Destruction of intermediaries by chemical and other means
4 Destruction of reservoir hosts
5 Proper disposal of manure
6 Clean stables

These methods individually or collectively would greatly reduce chances of infections

2 Serological Considerations

(1) Immunity

It has been shown during recent years that immune phenomena are elicited in animals as a result of infection with helminths just as with other groups of infecting agents In infected animals it has been shown that humoral and cellular forces come into play to bear against the parasites as in other types of infection These forces are manifested by the prese [illegible] permanent which are important [illegible] fect on l ke those i [illegible] est on can be diag [illegible] usual conventional [illegible] nother specificity [illegible] susceptible animal against infection

Immunity against helminths may be natural or acquired Natural immunity exhibited

in cases where an animal resists a particular helminthic infection, may be present life long or may be acquired with advance of age Total immunity or absolute resistance ... a susceptible species ... so seen that in many

Natural immunity

Acquired immunity

It has been argued that the parasites which occur in the lumen of the intestine or biliary ducts, never passing through the tissues and thus having no chance to come into intimate contact with blood or tissue fluids seldom give rise to any immunological phenomena but there has been a conflict of opinion on this point. It is reasonable to suppose that parasites which enjoy a circuit through the blood during their life cycle do call forth certain humoral changes, and parasites settling in tissues always stimulate certain changes in the tissues of the host, and consequent serological changes are responsible for the immunological reactions

Relation of location of worm to immunity

Chandler draws attention to a local immunity which is sometimes manifested In his opinion this local immunity is different from locally manifested general immunity or part of the immunity in general Parasites located in the skin or in the lumen or lining of intestines or biliary or other passages, are expected to give rise to this kind of local immunity, whereas those parasites imbedded in internal tissues or enclosed in body-cavities or lying in the circulation, are not likely to do so He postulates that there are two

Local immunity

Two phases of immunity

These immunological reactions are of great diagnostic value in diseases such as hydatid infection cysticercosis trichinelliasis and some other helminthic infections which can hardly be diagnosed in latent stages without the help of these methods

(2) Immunity in Diagnosis

As a rule the diagnosis of a helminthic infection is made from either the finding of the worms themselves, or their reproductive products namely eggs, embryos or larvae Sometimes this direct method of diagnosis is not possible and in these cases the serological methods are resorted to

As stated before, these serological and allied reactions depend on the development in the body of the host, of a specific immunity to an invading helminth The diagnostic methods are therefore applicable to those infections where the helminth is intimately associated with the tissues and blood of the host Thus hydatid disease, trichinelliasis and schistosomiasis are readily diagnosed in a high percentage of cases In other instances the reactions are not definite In the case of ascaris infection the worm need not be an actual parasite at the moment of performing the test, since contact with this worm can sensitize the persons handling or examining them, the sensitization being caused by the emanations from the worms

The antigens used for performing these tests are prepared in various ways They may be simple saline extracts of the ... and subsequently dissolved in saline ... tissues of the worm are used *e.g.*, of ... are used *e.g.*, hydatid fluid Some ... extracts evaporated to dryness and ... tracts of snails containing cercariae ... schistosomiasis.

Preparation of antigens

The four types of serological reactions adopted for diagnosis of helminthic infections are —

(a) Complement fixation test.

(b) Precipitin and flocculation test

The following table giving the classification of Trematodes is after Clay G Huff —

Class Trematoda

Subclass Monogenea (parasites of fishes amphibia turtles)

Subclass Aspidogastrea (parasites of molluscs and other cold blooded invertebrates)

Subclass Digenea

Order Prosostomata (hermaphroditic mouth usually surrounded by an oral sucker a ventral sucker may also be present cercaria with unforked tail)

Suborder Distomata

Family Fasciolidae

**Fasciolopsis buski* (greater intestinal fluke of man in Assam China)

Fasciola hepatica (sheep liver fluke, occasionally in man)

Family Opisthorchidae

**Clonorchis sinensis* (human liver fluke)

Opisthorchis felineus (common in dogs and cats of Europe occurs in man in Prussia, Poland Siberia India Japan French Indo-China)

Family Dicrocoelidae

Dicrocoelium dendriticum (a liver fluke of sheep incidental in man)

Family Plagiorchidae

Prosthogonimus macrorchis (in bursa Fabricii and oviduct of hens and ducks)

Ostiolum medioplexus (lungs of frogs useful for trematode study)

Family Echinostomatidae

Echinostoma ilocanum (intestinal fluke of rats rare in man)

Family Heterophyidae

Paryphostomum suprartyfer (in pigs and man)

**Heterophyes heterophyes* (intestinal fluke of man in Egypt China Japan Korea Formosa and Philippine Islands common in cats and dogs)

Metagonimus yokogawai (lesser intestinal fluke also found in dogs cats pigs birds)

Family Troglotrematidae

**Paragonimus westermani* (human lung fluke also found in cat dog tiger fox mink etc.)

Troglotrema salmincola (intestine of dog associated with salmon poisoning)

Suborder Amphistomata

Family Gastrodiscidae

Gastrodiscoides hominis (common intestinal parasite of pig in Orient sporadic in man in Assam Cochin China)

Family Paramphistomidae

Watsonius watsoni (rare intestinal parasite of man probably a parasite of monkeys)

Order Strigeatoidea

Suborder Schistosomata

**Schistosoma haematobium* (blood fluke which produces urinary schistosomiasis or bilharziasis in man)

**Schistosoma mansoni* (blood fluke which produces rectal or intestinal schistosom asis in man)

**Schistosoma japonicum* (blood fluke which produces oriental schistosomiasis or katayama disease in man)

*Those occuring in man are marked with an asterisk

The subject of treatment of parasites occuring in the tissues is of great importance and although considerable work has been done in this connection little progress has been made The difficulties arise out of many factors The absorption of the drug is essential for any action to be produced on blood and somatic worms and since most of the anthelmintic remedies are toxic to the host when absorbed in more than very small quantities the difficulty of finding a suitable drug to destroy the parasites is great Helminthic parasites may

occur almost in every organ and tissue in the body, and some are more easily reached than others The parasites lying in the liver are easy to reach since the drugs absorbed from the gut go through this organ first, and they reach it in high concentration The parasites lying in the lungs can be reached by drugs given by inhalation, and parasites in the blood can be reached by drugs from the digestive tract or by injection Parasites lying in the subcutaneous tissue, muscle, central nervous system, etc, must be reached indirectly by drugs circulating in the blood stream, which are therefore much diluted by the time they reach the parasites

The principal human somatic or extra-intestinal helminths important from point of view of anthelmintic treatment are, (1) flukes, parasitic in the liver, bile ducts, or pancreatic ducts, (2) lung flukes, (3) schistosomes located in the mesenteric blood vessels, (4) tapeworm cysts in muscles, liver and other viscera and the central nervous system, (5) filariae situated in lymph glands or ducts The embryos of trichinella worms during their wanderings in the blood stream and muscle tissue, before encystment in the muscle fibres may also be considered capable of anthelmintic treatment

The drugs which are considered effective against these parasites are practically the same as those used against intestinal helminthic infections During recent years a few more drugs have been added to the list, *e g*, antimony compounds, emetine, carbon tetrachloride, etc

(2) Schistosoma or Blood Flukes

There are three species of Schistosoma parasitic in man In the case of *S mansoni* of Africa and tropical America and *S japonicum* of China, Japan and Philippines, the eggs escape through the walls of the rectum greatly irritating that organ and also the liver In the case of *S haematobium* of Africa the eggs escape by way of the urinary passages, causing irritation to these After development in certain species of snails (usually of genus Bulinous) the larvae escape as bifid tailed cerceriae into stagnant water and usually infect man by actively burrowing through the healthy skin of people while bathing or washing There are separate male and female parasites living together in the blood vessels, and since they are slender and small they are not frequently seen unless especially searched for *post mortem* Most of the damage to the host is brought about by the eggs They stimulate the proliferation of adjacent host cells particularly the epithelium This results in papillomatous growths which cause obstruction necrosis sepsis, ulceration, and fistulae.

Signs and symptoms

Clinical Aspects The onset is marked by dermatitis produced by entrance of cerceriae into the skin It is followed by general symptoms such as remittent or intermittent pyrexia urticaria, abdominal pain, rigors etc There is pronounced leucocytosis with high eosinophilia at this stage

This stage is then followed by deposition of eggs which takes place in the bladder in the case of *S haematobium* and in the rectum in the case of *S mansoni* and *S japonicum*. The symptoms in this state therefore, depend on the seat of deposition of eggs which are responsible for severe local irritation

In many cases there are no marked symptoms while in other cases suffering may be very great and may ultimately end in death Early toxic symptoms such as fever, urticaria, etc may appear within a month of infection, in other cases symptoms may appear after from 3 months to two years or more The most striking symptom of deposition of ova in the mucous membrane of bladder is passage of blood at the end of micturition generally [illegible]
and [illegible]
and [illegible]
arour [illegible]
may [illegible]
of u [illegible]
may sometimes be deposited in such situations as kidneys, prostate seminal vesicles, rectum vagina lungs and brain, producing symptoms pertaining to the organ involved Urinary

Complications

fistulae opening in the perineum and posterior surface of scrotum are met with. The patient becomes anaemic wasted and debilitated. Ultimately untreated cases succumb due to one of the complications or superimposed infection

Diagnosis depends on finding ova with a terminal spine in the urine The presence of haematuria in endemic areas is suggestive Cystoscopic examination may help

Prognosis in mild infections is good In severe chronic cases it is bad, but treatment with antimony has greatly improved prognosis

Intestinal schistosomiasis—The localizing symptoms are diarrhœa, dysentery (Metazoal dysentery) tenesmus sometimes choleric diarrhœa. The course in infections with *S japonicum* is usually graver and more rapid t [illegible]
hepatolineal fibrosis may occur in a few cases.
terminal stages large growths in the passage causi[illegible]
g owths or fistulae in the anal region may result
tion cholæmia or superadded infection

Visceral schistosomiasis—Infection with *S mansoni* is frequently followed by splenomegaly This is common in Egypt and in some localities 20 per cent of infants have enlargement of spleen The condition resembles Banti s disease and is associated with anaemia, fever and wasting

The liver in early stages is enlarged and haematemesis is often present. The patient often dies of hepatic cirrhosis but death is usually caused by pulmonary complications The lungs may be involved even though there may be no clinical symptoms Prognosis is good in mild infections but with marked hepatic enlargement and ascites it is bad Diagnosis is made by finding characteristic ova in the fæces

On account of their location these parasites can only be reached *via* the blood stream, and are usually attacked by means of intravenous injection of anthelmintic drugs Very striking results have been obtained from the use of tartar emetic, which seems to have a specific effect on both the worms and the eggs. Some less toxic preparations of antimony have been recently tried with beneficial results, such as 'Fouadin', Anthiomaline etc.

(3) *Treatment with Antimony Compounds*

Schistosomiasis has been successfully treated by injections of tartar emetic. It was at one time thought that there was no means of destroying these parasites but Christopherson (1918) first tried, and showed that injections of the *double* [illegible]

and 1/2 grain (0 03 gm) for adults dissolved in 20 min. of [illegible] then diluted with an equal quantity of normal saline The dose is increased by half a grain up to 2½ grains (0 1 gm) unless a reaction is produced before that time Injections are given every other day, the dosage being kept between 2 to 2½ grains (0 13 to 0 16 gm) until 25 to 30 grains (1 7 to 2 0 gm) have been given This amount is usually sufficient to cure an adult, children are given [illegible] on the basis of 0 003 gm [illegible] over 100 000 [illegible] 12 injections [illegible] tartar emetic [illegible]
this cures [illegible] ment are most striking After a few injections the vesical pain and the scalding sensation disappear Blood is also absent from the urine though sometimes it *may persist* a little longer After the full course the urine becomes clear and normal in colour, this change probably corresponds with the cessation of the activities of the parasites and *the cure of the disease* This course is suitable for the

early stage of the disease when the patient is in a good state of health In old standing cases where they are weak and emaciated a less intensive course is desirable A slight coughing at the end of the injection is not a contra indication for continuing the treatment but if nausea vomiting abdominal pains giddiness and diarrhœa supervene the patient should be given a few days rest If more than 25 grains are required it is better to give a second course after an interval of a fortnight or more Lampe (1926) gave to out patients 150 to 250 ccm of a 1 0 per cent solution in 6 to 7 weeks to in patients a more intensive course of 200 to 240 ccm in 4 to 5 weeks was given As a rule no untoward symptoms occurred Lampe s conclusions are in accord with those of Christopherson and he considers 25 to 30 grains (1 6 to 2 gm) spread over 6 to 7 weeks the best treatment It is best to continue treatment for a week or 10 days after all ova and leucocytes have disappeared from the urine after centrifugalising

Usually after the injections have been given for a week or 10 days improvement begins In *S haematobium* the vesical pains disappear the urine clears up and so does the scalding sensation when the urine is passed In the case of *S mansoni* and *S japonicum* the blood in the fæces decreases fever disappears gradually and the asthenia and malaise improve In favourable cases eggs may disappear in 10 15 days In severe cases dead ova are passed intermittently for weeks and months after the parent worms are dead Degeneration of miracidia is seen early generally after about 12 grains have been given The ova become shrunken shrivelled and blackish and later do not hatch out in water When this stage is attained the parent worm is killed and the ova are sterilised *in situ* As a rule 30 grains (2 0 gm) of the tartrate administered in from 28 30 days form the curative dose The rapidity and permanence of cure are less dependent on the total amount of antimony administered than on a regular tri weekly series of injections Re-examinations of patients who have been given a course of 12 injections show that 80 per cent to 97 per cent are cured completely

Criterion of Cure

The criterion of permanent cure seems to be not yet standardised The general customary methods *i e* the microscopical examination for the eggs has not proved sufficient for all cases Some authors adopt eosinophilia as an indication for infection or cure where no other worm affection has been observed The Fairley test remains positive too long for it to serve as a control while on the other hand the method of testing by hatching of miracidia if any seem to be an improvement

Mode of action

The drug kills not only the adult worms but penetrates the shells and kills the ova deposited in the tissues This can be demonstrated by adding tartar emetic to 6 ccm of warm water at 133°F to which a little urine containing ova has been added It is found that if the antimony salt is not added the ova begin to hatch out in 4 to 5 minutes and that most of them have hatched out in an hour If however a grain of tartar emetic is added to the water only half the ova hatch out and a good many are found to be dead half in and half out of the shell If the concentration is further increased very few embryos hatch out and even the few found swimming do not survive long Under the microscope one can [illegible]
[illegible]
emetic *in vitro* was greatly enhanced in the presence of human serum Everything points to the fact that tartar emetic is a powerful therapeutic agent in the trea

ment of all schistosome infections Even in patients undergoing surgical treatment a course of antimony is desirable

Hamilton Fairley (1924) was of opinion that tartar emetic in a proportion of cases merely reduced the parasitic level and converted cases of frank clinical schistosomiasis into passive carriers in whom ova are shed in small quantity and at such irregular intervals as to escape detection on one or more isolated examinations He tried the drug in *S spindalis* in goats and got results which suggested that the antimonyl tartrates were less effective than emetine. These results however, cannot be applied to the human disease and investigations in Egypt show that emetine is not as effective as tartar emetic Day (1924) showed that comparatively small doses of antimony (25 grains of tartar emetic) are required to kill the ova present in the tissues, and that reappearance of ova in the urine after small doses, is due to the fact that a sufficient quantity of the antimony salt has been given to kill the ova but not the adult parasites, which have only been temporarily affected by these small doses Relapses are due to lack of judgment with regard to dosage, if a sufficient quantity of antimony compounds are given no relapses occur It has been shown that 20 per cent of cases relapse after 2 years with 0 7 gm, 15 per cent have viable ova after 1 3 gm, after a full course of 2 gm 3 5 per cent still remain infected The usual cure rate is 79 per cent *In uncomplicated cases as a rule 25 grains (1 6 gm) produce* a complete cure but the total quantity of the drug varies largely in different individuals and every case should be treated on its own merits Even in the worst cases the mortality is reduced to half

es

With the extension of the [illegible] defects were revealed which make mass tr[illegible] rate the long treatment on account of [illegible] reatment even with a large dose make[illegible] always bear in mind the technical dificultres, such as the trouble of preparing the solution before use in freshly distilled water on each occasion Further on storage the toxicity of the solution may increase The impossibility of injecting *it intra*muscularly necessitates emetine treatment in the case of small children and patients with bad veins To overcome these difficulties sodium antimony tartrate was at first tried and later Fouadin was evolved

Fouadin Clinical trials have shown that preparations in which antimony is present in a trivalent form as in tartar emetic, were effective in schistosomiasis A compound named antimosan *which could be administered intramuscularly* had a remarkable action in schistosomiasis This drug is well tolerated intramuscularly though it was not entirely painless, it could also be given by the intravenous route and was less toxic than tartar emetic It is superior to stibenyl and stibosan These observations led to the preparation of fouadin (neoantimosan)

Purified oxide of *antimony is used in its* preparation *and it contains* 8 5 mgm of trivalent antimony per ccm It is isotonic with the tissues and is neutral in reaction the sodium salt is used instead of the potassium salt in its preparation. Animal tests show that in therapeutic doses it is not toxic In 80 patients of which 68 were infected with *Schistosoma haematobium* 7 with *Schistosoma mansoni* and 4 with mixed infection of both complete cure was obtained in all except 5 cases Total dosage required was from 40 to 50 ccm of fouadin per 60 kilo body weight given in 9 to 10 intramuscular injections The fact that the action of antimony continues even after the completion of the treatment could be seen from the progressive degeneration of the eggs In 3 5 per cent of all the cases headache and nausea and in 5 per cent vomiting *in the second* half of the treatment were observed

The absorption of fouadin solution administered intramuscularly is completed within 10 minutes. Fifty per cent of antimony administered is eliminated through the urine and only approximately 4 per cent through the faeces. *Absorption*

Dosage

Khalil (1931) used fouadin in the treatment of Schistosomiasis on a mass scale in the following manner: injections were chiefly given intramuscularly, 100 ccm ampoules being used and a special apparatus for rapidly filling the syringe was employed. The patients were asked to rest for 2 hours after the injection. The doses in an adult of 60 kilo were: first day 1.5 ccm, 2nd day 3.5 ccm, 3rd day 5 ccm and then 5 ccm every other day until a total of 40 ccm was administered. If living ova were still present, the treatment was continued but more than 11 injections were rarely necessary. The treatment lasted 2 weeks as compared with 4 weeks with tartar emetic treatment. In mass treatment practice, fouadin therapy was usually extended to 19 days and that with tartar emetic to 29 days. In favourable cases the treatment was shortened by giving 4 or even 5 injections on successive days. Vomiting occurred in 0.36 per cent and abscess formation was seen only in two instances among approximately 20,000 injections. Bradycardia was present in some cases but far less than after antimosan; the pulse was not reduced by more than 12 beats per minute. On the whole it could be said that fouadin is tolerated better than tartar emetic and its effect on the eggs is identical.

Intramuscular injections of fouadin are practically painless; the only disadvantage is that fouadin is a more costly drug than tartar emetic.

Cases of vesical schistosomiasis suffering simultaneously from cutaneous leishmaniasis require a great number of fouadin injections to influence the latter complication in addition to the former, 13 to 24 intravenous injections being given. The high dosage is well tolerated and the urine is freed from ova at the conclusion of the treatment. Intravenous therapy does not have any advantage over the intramuscular route either as regards the duration of treatment or the total quantity of the drug necessary.

Standard course

The standard treatment evolved in Egypt has proved successful. Adults are given 9 to 10 injections. The first two injections given on successive days being of 1.5 ccm and 3 ccm respectively. The subsequent injections are 5 ccm each and given every other day. Khalil has attempted to shorten the duration of treatment, commencing with a dose of 3.5 ccm followed by doses of 5 ccm the first 3 or in suitable cases 5 injections being given on successive days and the remainder every other day till a total of 8 to 11 injections or more are given.

The drug is contra-indicated in hepatic cirrhosis, acute pyelitis, cardiac disease, and pregnancy. *S. haematobium* infestations respond more easily than those of *S. mansoni*.

In comparing the efficacy of tartar emetic with fouadin the quantity of antimony used should be borne in mind. According to the dosage scheme of Khalil the following figures are of interest:—

	No of injections	Time	Total dose	Mgm of Sb
Fouadin	9	19 days	43.5 ccm (1 ccm = 8.5 mgm Sb)	370
Tartar emetic	12	28 days	1.35 gm (36.5% Sb)	493

[...]emetic therapy more antimony is used

Other Antimony preparations In recent years the new preparation *anthiomaline* has been used in North America and remarkable results are reported This preparation is better tolerated than tartar emetic and is said to be effective in schistosomiasis It is supplied in 2 ccm ampoules of a 6 per cent solution containing 0 02 gm of antimony The initial dose is 1 5 ccm and the maximum dose 4 ccm, a total of 65 ccm is given in an adult. In children of twelve years the initial dose is 0 5 ccm and the maximum dose 2 ccm It is best given by the intravenous route on alternate days

Stibophen is a 6 3 per cent solution of sodium antimony bis-catechol 3 5-disulphonate, which can be used by the intravenous and intramuscular routes The initial dose in adults is 1 5 ccm, 3 5 ccm on the second day 5 ccm being the maximum dose, a total of 40 to 75 ccm is given in an adult For children the initial dose is 0.5 ccm and 3 5 ccm is the maximum dose and a total of 47 5 ccm is given An average course lasts 29 days

Bathing in and drinking of water of rivers, ponds and canals should be prohibited People should be warned against wading through or fishing in infected localities Swamps, when slightly brackish, are safe Drinking water should be boiled The diffusion of disease should be prevented by prohibiting soiling of water with excreta, especially of infected individuals The intermediary mollusc and the free cercariae should be attacked by periodic drying of irrigation channels etc, and the use of c[illegible] as sulphate of soda tablets should be used [illegible] ing water lysol, creolin, or cresol (1 in [illegible] ordinarily used for sterilizing water (1 in a million), has no [illegible] living cercariæ Lime (1 in 1,000) is effective in exterminating the intermediary host and kills cercariæ Application of steaming jet and copper sulphate (1 in 20 000) are toxic to snails Eggs remain viable in faeces for ten days Mass treatment will help to eliminate carriers; educational propaganda is important. It should be remembered that the disease occurs in dogs and other domestic animals and snail vectors live in inaccessible situations In heavily infected snails, the genital glands are infected and they do not propagate.

Intermediary molluscan hosts *Bulinus contortus* *B dybowski* (Egypt and North Africa) *B innesi* (Sudan) *B truncatus* (Palestine), *B forskali* (Mauritius and Kenya) *B globosus* (Sierra Leone, Nyasaland) *Physopsis africanus* (Natal) *B tropicus* (S Africa) *Isodora ovoidea* (Zanzibar) *Physopsis nasuta* (Kenya) *Planorbis dufourii* (Portugal and Morocco) In the genus *Bulinus* the body of the snail contains red haemoglobin The shell is spiral not operculated and the opening *sinistral* (*Manson Bahr*)

(4) Treatment with Emetine and other drugs

Although emetine hydrochloride does not kill the bilharzial cercariæ (*S spindalis*) *in vitro* in 1 in 100 dilutions, in the presence of serum it kills them in dilutions of 1 in 160 000 The lethal effects of both emetine and tartar emetic are greatly enhanced in the presence of human serum

[illegible] of emetine have been used in the [illegible] d have succeeded in [illegible] 1 grain (0 06 gm) [illegible] a second series of 6 injections is given In children, doses of ½ gr (0 03 gm) are often sufficient No living parasites or ova can be found after the fifteenth injection Emetine is specially indicated in patients who are intolerant to antimony The drug acts on the ova which show degenerative changes, it also kills the adult worms gradually Diamantis (1918, 1921) reported a number of cases of *S haematobium* infection which were cured by emetine injections He gave the drug intravenously in doses of 0 12 gm 10 to 12 injections at intervals of 3 to 5 days, 0 8 to 1 05 gm of emetine in all, produced a cure It is also effective against *S mansoni* In

urinary schistosomiasis the length of treatment and dosage are both important Harkness (1920) gave a total of 14 grains (1 0 gm) and a further total of 20 gr without effecting a cure Cawston (1922) recommended emetine dissolved in 20 minims of a 1 per cent solution of carbolic acid intramuscularly for 8 consecutive days and then thrice weekly for three weeks Cardiac depression occurs in the second and third week but it can be avoided by giving digitalis He gives emetine in preference to antimonyl tartrates in children and young people in whom it is difficult to get into veins According to him curative doses of emetine for schistosomiasis is double that given for amœbic dysentery *S japonicum* has been cured with emetine injections starting with ½ grain and increasing the dose to 2 grains daily, as toleration developed two courses of 15 grains each with an interval of one week are recommended Cawston (1926) held that unless very large doses of emetine are given uninterruptedly emetine cannot be depended on in schistosomiasis Such doses are very risky and are not to be recommended

Emetine periodide

[illegible] *haematobium* [illegible] es not produce [illegible] remetine given [illegible] ted the use of antimony along with that of emetine but experience shows very little advantage in such a mode of treatment. Khalil suggests that as emetine is a depressant drug its use in Schistosomiasis should be limited to those cases where amœbic dysentery is simultaneously present

Emetine with antimony

It will be seen from the above review of the literature that emetine should only be used in those cases of schistosomiasis which are intolerant to antimonyl tartrates or in children in whom it is difficult to find the veins In cases of intestinal schistosomiasis complicated by amœbic dysentery emetine is indicated Its dosage should be carefully regulated and if toxic symptoms appear it should not be continued

Emetine in other helminthic infestations Emetine has been found useful in infestations of the liver with *Fasciola hepatica* and *F gigantica* Kikalko and Imamura (1920) found daily injections of emetine useful in clonorchis infections

Emetine injections have been recommended in the treatment of dracontiasis Tournier (1923) treated 17 cases of this infection by giving emetine intravenously and by the mouth with good results This has not however been confirmed by other observers Emetine in daily injections is said to be valuable in ameliorating symptoms produced in paragonimiasis but these cases need careful watching for the onset of toxic symptoms Potassium iodide and tartar emetic injections are preferable

Emetine preparations have been tried against filarial infections especially of *W bancrofti*, but without effect

(5) Liver, Intestinal and Lung Flukes

Liver flukes

Clonorchis sinen [illegible] parasite about half [illegible] the intestine with [illegible] larvae encyst in cer[illegible] cooked infected fi[illegible] where fish is hal[illegible] It produces thicke[illegible] Rarely it may be [illegible] blindness and epig[illegible]

jaundice anasarca and cachexia are met with ending in death after several years There is leucocytosis up to 30000 eosinophilia upto 40 per cent Eggs may be found in the duodenal juice removed by a duodenal tube

Treatment is unsatisfactory but intravenous injections of fouadin (1.5 to 5 ccm (10 or more) are useful, Gentian violet has also been tried In daily doses of 3 grains (0 10 gm), in divided doses an hour before meals it is quite effective *In children dosage is calculated on basis of 0 01 gm per year of age* Non surgical drainage of bile (continuous) by duodenal tube gets rid of the eggs and toxic matter and gives temporary relief

Fasciola hepatica is the cause of liver rot in sheep it occurs in man in Central Europe Syria England South America and China The parasite *is found in the portal veins* and in subcutaneous abscesses, it may produce epileptiform convulsions Infection occurs by eating water plants on which the cercariae encyst from infected streams. There is no effective treatment but emetine injections and neostibosan may be beneficial

Opisthorchis felineus occurs in Persia Siberia Philippines, etc., in man dog cat and pig In man it produces the same symptoms as *Clonorchis* but it is not markedly pathogenic

Fasciolopsis buski is a large flat worm an inch or more in length and about half wide It occurs in man pigs dogs and other animals in India, Assam China and Malaya. Its embryos develop in snails and after development the larvae leave the snail and encyst on water vegetation such as water caltrop infection resulting from eating such vegetation uncooked The parasite is found in the small intestine rarely in the stomach, and produces alternate diarrhoea and constipation with offensive stools œdema of face legs and abdominal wall Symptoms may resemble that of peptic ulcer B naphthol carbon tetrachloride tetrachlorethylene and hexylresorcinol in usual doses are effective

Heterophyes heterophyes is a very small intestinal fluke hardly larger than a pin head It reaches the human host by encysting in the flesh of certain species of fish which is often eaten raw This infection is also common only in the Far East Enormous numbers of these parasites stick to the mucous membrane of the small intestines giving rise to diarrhoea symptoms of cardiac beri beri occur on account of eggs occuring in myocardium Effective treatment is by thymol or by oleoresin of male fern

Metagonimus yokogawai occurs commonly in Balkan States and in the Far East, Korea and Japan The parasite is found in upper part of small intestines of man, dog and cat The metacercaria encyst under scales of fish which is eaten raw in Japan and may give rise to diarrhœa Treatment with thymol and aspidium is effective

Gastrodiscoides hominis normally a pig parasite occurs in man in India, Assam and *Indo China. Its life history is not definitely known* but is probably similar to that of *Fasciolopsis buski* Treatment with tetrachlorethylene is effective

Paragonimus westermani is met with in the Far East, India and U S A It occurs in man wild canidae and mink This fluke is rather egg shaped almost as thick as wide reddish brown in colour and about half an inch in length After development in certain species of snails the larvae encyst in fresh water crabs and infection results from eating uncooked or undercooked crabs a practice which is common in certain parts of Japan where the infection is prevalent Young flukes escape through the host's intestines into the abdominal cavity penetrate the diaphragm and then enter the lungs Other organs may also be the seat of development Small brown spots occur in lungs and scattered burrows are visible Eggs are coughed up in sputum in enormous numbers and it is often *associated with tuberculosis of lungs eggs also occur in* fæces and rarely in spinal cord where they produce transverse myelitis Hundreds of these flukes have been found in psoas abscesses Symptoms start with distress in chest cough and brown rusty sputum containing thick operculated eggs irregular haemoptysis may occur Dull pain in the abdomen diarrhœa, enlargement of liver clubbed fingers epileptic symptoms hemiplegia aphasia visual disturbance and cutaneous ulceration may occur This condition can be easily diagnosed by finding eggs in sputum and *faeces and leucocytosis*

Treatment is unsatisfactory but seven day courses of injections of emetine 1 gr each intramuscularly may do good Intravenous injections of 0 5 to 1 0 ccm of a 4 per cent daily and intramuscular injections of the same intervals until the ova show 7 to 17 days The symptoms improve d with caution Lipiodol injections into be burnt and sale of crab forbidde

4. Tapeworms of Man

Tapeworms infect man both as adults and larvae. Many species have been reported as attacking man. However, there are only four adult tapeworms which may be considered normal human parasites, namely, *Diphyllobothrium latum* the fish tapeworm, *Hymenolepis nana*, the dwarf tapeworm, *Taenia saginata*, the beef tapeworm; and *Taenia solium*, the pork tapeworm.

(1) Classification

The following table giving classification of Cestodes is after Clay G. Huff (A Manual of Medical Parasitology).

Class Cestoidea, Platyhelminthes
  Subclass Cestodaria (in fishes)
  Subclass Cestoda
  Order Pseudophyllidea

FAMILY DIPHYLLOBOTHRIIDAE
- **Diphyllobothrium latum* (broad fish tapeworm of man)
- *Diphyllobothrium erinacei* ("Mansoni" occasional larval infections in man)
- *Diphyllobothrium cordatum* (accidental parasite of man)
- *Diphyllobothrium mansonoides* (probably adult of *Sparganum proliferum* of man)
- *Diplogonoporus grandis* (rare parasite in Japan)

  Order Tetraphyllidea (in fish, amphibia, reptiles)
  Order Cyclophyllidea

FAMILY TAENIIDAE
- **Taenia solium* (pork tapeworm of man)
- **Taenia saginata* (beef tapeworm of man)
- *Taenia pisiformis* (cats and dogs)
- *Taenia ovis* (dogs)
- *Taenia hydatigena* (dogs)
- *Taenia taeniaeformis* (cats)
- **Echinococcus granulosus* (hydatid in sheep, cattle, man)
- *Multiceps multiceps* (gid worm, rare in man)
- *Multiceps serialis* (dogs)
- *Multiceps gaigeri* (dogs)

FAMILY DAVAINEIDAE
- *Raillietina tetragona* and other spp. (chickens)
- *Raillietina asiatica*, *Raillietina celebensis*, *Raillietina madagascariensis* } rare parasites of man

FAMILY ANOPLOCEPHALIDAE
- *Bertiella studeri* (monkeys, chimpanzees, man)
- *Moniezia expansa* (sheep, cattle)

FAMILY HYMENOLEPIDIDAE
- **Hymenolepis nana* (dwarf tapeworm of man)
- *Hymenolepis diminuta* (rats, mice, man)

FAMILY DILEPIDIDAE
- *Dipylidium caninum* (dogs, cats, man)

*Asterisks indicate that larval infection are common in man.

(2) Intestinal Tapeworms of Man

Diphyllobothrium Latum. The fish tapeworm is a very large, broad, flat worm reaching a length of 15 to 30 feet or more. It has a slender head and neck, the former with two longitudinal sucking grooves instead of the usual four rounded suckers. The segments are

Diphyllobothr... lum

broader than long and have a rosette shaped uterus containing the brown eggs near the centre This worm produces eggs usually in large numbers which resemble the eggs of flukes in that they are provided with an inconspicuous operculum at one end but the shell is much thinner The intermediate hosts are successively water fleas (Cyclops) and fish. Infection can occur only when undercooked infected fish is eaten.

Generally the digestive symptoms caused by this worm are not many and may not be even noticed Abdominal pain loss of weight or other symptoms are the same as occuring in other *tænia infections*

This parasite however, has been associated with pernicious type of anæmia, of a severe degree Although the infection is very common in many countries anæmia develops only in a small percentage of the cases The anæmic condition improves after liver therapy even without the removal of the worms There has been much discussion with regard to the role of *diphyllobothrium* in the production of this anæmia during recent years, but our knowledge on this point is still not definite

Hymenolepis nana is a very minute tapeworm parasitic in rats and mice as well as in man It is seldom as much as an inch in length and very slender When expelled in the fæces it resembles a little strand of mucus It is undoubtedly the commonest human tapeworm and *is often present in large numbers* Unlike other human tapeworm, it undergoes complete development from egg to adult without change of host. The larval stages are developed in the intestinal villi as the eggs are shed from the segments while still inside the body of the host Diagnosis can be made by the usual fæcal examination If *the eggs are discovered in the fæces and the six little hooks which are* characteristic of most tapeworm eggs are seen it is very commonly incorrectly diagnosed as a *Taenia* infection and the physician is at a loss to know why he is unable to expel any part of such a worm by the anthelmintics which are always efficient in removing at least the greater part of *Taenia*

The parasite in heavy infections may produce nervous and digestive symptoms especially in children who suffer from pain diarrhoea, epileptic attacks and insomnia

Taenia saginata is in most countries the commonest large tapeworm of man. It reaches a length of from 10 to 15 feet or more the ripe detached segments are shaped like pumpkin seeds and are about an inch in length the head is provided with four suckers but is devoid *of hooklets and is about the size of a medium-sized pin head* The detached segments pass out with the fæces only occasionally rupturing before leaving the body so that one cannot depend on diagnosing the infection by searching for eggs in the fæces The worm develops into the larval bladderworm stage in cattle and human infection results from eating infected *beef which has not been thoroughly* cooked *and still retains its* red colour

T ... s ... similar to *T saginata* but is smaller and has a head which is armed ... he ripe segments which are passed ... ose of *T saginata by the* number ... the segment In *T saginata* there ... *olium* there are only 12 or less The ... comes from eating raw or under- ... parasite than the *beef tapeworm* ... opment in man as well as in pigs and this may happen when a ripe segment is regurgitated into the stomach. If this worm is found it is advisable to give treatment at once

The presence of the parasites in the intestines causes no distinct lesion in the early stages Diarrhœa and hunger pains not infrequently develop and loss of weight may occur Appendicular colic has been reported due to clogging of the appendix with shed segments (proglottides) The parasites possibly produce some toxic substance which may *be the cause* of digestive disturbances and neurosis seen in a few cases

All tapeworm infections are difficult to cure because the heads of the worms are deeply imbedded in the mucous membrane and are often not reached by the anthelmintics used The main bodies of the worms are paralysed or killed and the movements of the intestine tend to drag them away, *commonly breaking* them off just behind the head which then soon reproduces the whole worm again. It is for this reason that careful preparation of the patient by means of a liquid

diet and purges is necessary in order to increase the chances of dislodging the head

Preliminary Preparation

The preliminary preparation of the patient in case of tapeworm infection must be thorough The routine of treatment is described under aspidium The patient should keep in bed after taking the drug The stools should be passed in a chamber pot half full of water so that the worm can be recognised this should be examined carefully to see if the head has been passed In case the head is passed no more anthelmintic should be given but the stools should be watched to make sure that there is not a multiple infestation If only segments have been passed the treatment should be repeated in full after 10 to 14 days If there is doubt about the expulsion of the head it is best to wait for 8 to 10 weeks watching the stool in the meanwhile for reappearance of segments If no ova or segments can be detected the head has been expelled If *T solium* is found prompt treatment should be given since there is danger of cysticercus infection

The cestode group of anthelmintics includes the phloroglucinol series *i e* male fern which is entirely successful in dwarf tapeworms and also kousso and kamala, pomegranate bark or its active principle pelletierine which should be employed when male fern fails the active principles of areca nut (arecoline) peps or pumpkin seeds are remedies against *T saginata* Other less important agents are cocoanut, butylchloral hydrate oil of turpentine brayera etc Multiple doses of caprocol crystoids are effective (See Hexylresorcinol)

Carbon Tetrachloride and other drugs

In recent years carbon tetrachloride tetrachlorethylene hexylresorcinol gentian violet (medicinal) sostol (an acridine compound) have all been used and seem to be almost as effective as the time honoured remedy filix mas These drugs are preferred now a days as the unstable nature of the active principles of male fern tends to make the results uncertain and attended with toxic manifestations

(3) Larval Tapeworms in Man

Larval tapeworms (bladderworms coenuri or hydatids) in domestic animals may be of importance from two points of view namely the health of the animals themselves and the danger of transmission to man.

Cysticercus bovis

Cattle are subject to infection with the cysticerci of *Taenia saginata* known technically as *Cysticercus bovis* producing a condition popularly spoken of as measles The bladder worms about half an inch in length are imbedded in muscles. When under done meat containing these parasites is eaten by man *Taenia saginata* infection results.

Cysticercus Cellulose

Hogs are parasitised by the cysticerci of *Taenia solium* technically called *Cysticercus cellulose* These resemble the bladderworms of cattle but are frequently present in enormous numbers These bladderworms will develop in many other animals also including man, but the hog is the most frequent host and the most important from the standpoint of human infection

[illegible]

become calcified (in 3 years or longer)

They inhabit the small intestines especially the jejunum, less so the duodenum an rarely the ileum where they attach themselves by powerful buccal armature to the mucou membrane and injure the intestinal wall *They thus obtain nourishment and suck bloo* producing anaemia and other symptoms

There are two species *Ankylostoma duodenale* and *Necator americanus* bot similar in size and general appearance habits and life cycle. They are about 1/ to 2/3 inch in length slender and reddish in colour when living but dirty white whe dead as after being expelled by anthelmintics The female produces a never ending stream of eggs which pass out in the fæces. In the body of the host the embryos in th egg do not develop much but on leaving it and under suitable conditions the embryo hatch out in two days This organism feeds voraciously on organic matter and in tw weeks it moults twice The larvae then become torpid and in this condition are easily killed Man is infected by these infective larvae boring through the healthy skin of the foot legs or other parts of the body coming in contact with them After entering the body they are carried by the blood stream to the heart and then to the lungs, they then bore into the alveoli From here they make their way up the bronchial tubes and trachea to the throat are swallow... weeks after infection
The forme...
the latter i...
Africa south of the Sahara, Southern Asia and Australia

The site of penetration of the skin by hookworm larvae may become the seat of dermatitis known as 'ground itch' especially in the case of *Necator americanus*

There may be hundreds of the worms in the intestines without producing any symptoms whatsoever Grave symptoms are not common but may occur in some cases In the tropics in patients suffering from dyspepsia, debility and anaemia the physician should think of hookworm infection and if detected, treatment should be given at once If infection is allowed to persist severe anaemia may result The essential symptoms of ankylostomiasis are progressive anaemia which if unchecked may produce fatty degeneration of the heart and death from collapse Oedema may be localised or general

Some patients complain of persistent epigastric pain and appetite may be defective and taste may be perverted diarrhœa (with imperfectly digested food) may occur or there may be constipation The stools are reddish brown but seldom contain pure blood Temperature may be constantly subnormal or there may be irregular or intermittent fever Later pallor of skin puffiness of face, lassitude shortness of breath vertigo dimness of vision mental depression and apathy haemic murmurs and retinal haemorrhages may occur

Subacute infections may occur especially in Europeans

Diagnosis is easily made by finding ova in the stools Floatation method and concentration technique may be used and test made for occult blood The grade of infection runs from 1 000 or more worms

These symptoms develop insidiously The anæmia is of the secondary type hypochromic and microcytic in character

There are different views regarding the manner in which anæmia is produced in this condition —(1) Chronic loss of blood through feeding of the parasites and hæmorrhage from the spots from which the worms release their hold (2) Hæmolytic toxin produced by the worms (3) Unfavourable dietetic influences by interfering with the digestion of *proteins (4) Bacterial infection through the portals opened up by the bites of the worms*

Ankylostoma duodenale causes a more severe degree of anæmia in the host and is less susceptible to anthelmintic treatment than *Necator americanus*

Infestation with necators is common in Southern India, in northern parts of India ankylostoma is common, infections are generally of mixed types Milder infestations such as those containing 100 to 500 eggs per gramme of fæces are harmless Experienced workers say that about 100 worms are required to produce any pathogenic eff... be present for at least six months to produce ... nt when severe degrees of a... ll number of worms such as 1(...

They therefore advise wholesale treatment Infections are present both in tropical and subtropical zones all over the world In India the heaviest infestations are found in places which experience heavy rainfall *e g* Assam Burma and Malabar Moderate infestations are encountered in Bengal Behar the United Provinces and the Southern Bombay coast Eighty to 100 per cent of infections occur in the country and 91 per cent in the urban areas with an average only of 10 worms

Treatment—Tetrachlorethylene oil of chenopodium carbon tetrachloride and thymol are drugs which enjoy the reputation of being almost specific in the treatment of hookworm infestation (see description of these drugs) Recently hexylresorcinol in 1 gm doses has been found to be a very promising drug Tetrachlorethylene and hexylresorcinol have become the drugs of choice After an interval of 10 days after the treatment the stools should be re-examined and if ova are found the treatment is repeated During convalescence after severe

cases The diet should be balanced and liberal in all its constituents

Creeping eruption—A linear eruption caused by the larvae of certain cat and dog hookworms The larvae penetrate the skin and eruption progresses at one end larvae being seen just ahead of the lesion The eruption is frequently seen on legs of children Treatment is by freezing the advancing lesion with ethyl chloride

Prophylaxis—Faecal contamination of soil and water should be prevented by having proper latrine arrangements and disposal of night soil Larvae want air and earth for development and if fresh stools are not mixed with earth

(3) Ascariasis

Ascaris lumbricoides is a very common human parasite inhabiting the jejunum The worms lie motionless and curled up in bundles so that the gut is stuffed up with them Toxic symptoms produced are due to *ascaron* a mixture of albumoses and peptones (What is probably the same species is a very common pig parasite) Its eggs pass out of the body and an embryo

ale ascaris may

are discharged

s time Infec

Ascaris lumbricoides

In China and Japan where night soil is used for cultivating gardens the eggs are ingested with uncooked vegetables in India, polluted earth or drinking water is the usual vehicle When swallowed the eggs hatch out and the embryos burrow into the mucous membranes make their way to the lungs, and thence reach the intestines in the same way as do larval hookworms The adults are eight to twelve inches or more in length and as large around as a lead pencil Sometimes no males are present in which case unfertilized eggs are passed, different in appearance from the fertile eggs

The larvae in passing from the capillaries incite a local allergic reaction This allergic exudate may cause consolidation in the lungs and thus cause ascaris pneumonitis

The passage of the worm gives rise to intolerable itching at the anus and vomiting of the worms may produce œdema of glottis There may be little or no symptoms, on the other hand, in children, it may produce interference with nutrition, capricious appetite, restlessness, foul breath and mental irritability, vague abdominal pain, nausea, and severe urticaria

As a result of migratory habits the adult worms may penetrate into any accessible passage and cause serious local symptoms *e g*, into the appendix, bile ducts gall bladder, pancreatic duct, nasal sinuses, middle ear, and larynx In the intestines the adults cause little local injury When numerous they tend to aggregate in clumps and may cause obstruction Nutritional disturbances may be produced as a result of inhibition of the digestion of proteins by pepsin and trypsin A substance of the order of primary albumose named *'Ascarase'*, found in the tissues of the worms, combines with these ferments and inhibits their action on proteins Infection with ascaris is very prevalent in many insanitary tropical countries and is often associated with ankylostomes

Diagnosis is made by microscopic examination of the stool if necessary, by the egg concentration method Eosinophilia is often present Cutaneous reaction to ascaris antigens are of little use but the 'scratch test with powdered ascaris is more reliable but it is often negative X rays are useful

Santonin and oil of chenopodium are usually effective The day before the treatment a saline purgative such as sodium phosphate or sulphate, or magnesium sulphate may be given The following morning the anthelmintic is [illegible] sually combined with calomel is given at night, norning The worms may not be expelled till these drugs produce toxic effects

In recent years hexylresorcinol (crystals in gelatine capsules) has been found to be the drug of choice because of its efficiency, safety and convenience of administration The dose is 1 gm for an adult and for children 0 1 gm for each year up to ten years The drug is administered on an empty stomach, and food is withheld for four hours It is, however, a costly drug and hence not suitable for mass use, in comparison with a combination of santonin and chenopodium, the results in the latter cases being almost equally satisfactory It is advisable to repeat the treatment after a week or two to make sure that all the worms have been expelled

Recently phenothiazine has been recommended in 8.0 gm doses as an effective drug in the treatment of ascariasis (see description later on)

Prophylaxis consists in good sanitation Vegetables, grown in places where night soil is used as manure, should not be eaten raw Eimeran, a coal tar derivative containing sulphur is said to be effective in killing ascaris eggs, and may be used in latrines as an antiseptic

(4) Trichuris, Strongyloides and Enterobius

Trichuris trichiura is a whip shaped worm, the head end being drawn out into a fine filament, comprising over one half the length of the worm Its total length is about two inches It inhabits principally the cæcum and adjoining parts of the large intestine as well as the appendix, and affixes itself very firmly by threading its head into the mucous membranes Its position far back in the intestinal tract and its firm fixation account for its resistance to anthelmintics Embryos develop inside the eggs after they are passed and infection results from swallowing such ripe eggs Polluted water and vegetables act as vehicles for the eggs, but flies also carry them After entering the body the eggs hatch and direct development occurs without migration to the lungs Trichuris infections are as a rule incurable

The infection is generally symptomless but in heavy infection the symptoms may be epigastric pain, vomiting constipation or mucus diarrhœa, fever, flatulence, anorexia and loss of weight

Many drugs have been used in the treatment of *Trichuris trichiura* or whipworm infections but none except one has been found to be satisfactory Santonin and calomel 2 to 3 gr of each, oleo resin of aspidium, thymol in doses of 15 gr, tetrachlorethylene, carbon tetrachloride, oil chenopodium with a saline purgative afterwards have been found only partially efficacious, hexylresorcinol in doses of 1 gm without any after purge does not seem to be any superior The only known drug which is efficacious against whipworm is *leche de higueron*, or hugerolatex, the sap of *Ficus laurifolia* and *F doliaria* in South America The dose for an adult is 2 oz (60 ccm) taken preferably on an empty stomach followed by a glass of water It is most successful if a saline purge is taken on the previous evening and again two or three hours after the administration of the anthelmintic

Treatment

Strongyloides stercoralis is a very minute parasite little over 2 mm long and extremely slender inhabiting the duodenum Its eggs hatch before leaving the body of the host so that only embryos are ordinarily found in the fæces The embryos either develop directly into long slender infective larvae or the latter in turn produce the infective lar intestines in the same the males are very r membranes and the widely distributed in as hookworm or asca anæmia may sometim worms or independen females burrow into

Strongyloides stercoralis

While many drugs have been tried gentian violet (medicinal) only has proved to be an effective strongyloidicide The dye is given before meals in enteric coated tablets 1 gr thrice daily up to a total of 50 grs For refractory cases, 2 ccm of a 1 per cent solution is put into the duodenum by a tube. For pulmonary infection and for severe late stage intestinal cases, intravenous administration of 0 5 per cent aqueous solution in doses not exceeding 25 ccm on alternate days is resorted to for a period not exceeding 10 days For such therapy the patient should be in a hospital and under careful supervision

Specific action of gentian violet

Enterobius vermicularis the threadworm or pinworm inhabits the colon cæcum and lower portion of the small intestine. It is probably the commonest human parasite The females are about one half inch in length slender white and sharply pointed at both ends The males are much smaller and are usually overlooked The adult female when [illegible] nails of children [illegible]atching When [illegible] hatch pass to [illegible] may cause no [illegible] except pruritus ani, which may lead to eczema as a result of constant scratching Abdominal pain and convulsion in children may sometimes be due to these worms. Migration of the worms up the vagina and uterus may set up salpingitis, etc Appendicitis may in rare cases be due to these worms

Enterobius vermicularis

[illegible] e renders them to some extent usually enemata are necessary [illegible] autions to avoid reinfections Since the adult female worms escape when filled with fertile ripe eggs, the infection tends to die out soon in the absence of reinfection It is essential with any course of treatment to prevent reinfection This is best accomplished by tying a cloth well smeared with zinc oxide ointment or unguentum hydrargyri over the anus and between the buttocks This should be replaced morning and

Treatment

elephantiasis of the limbs a fair proportion of the cases showed genital affections like hydrocoele elephantiasis of scrotum penis vulva and breast and chyluria

From a study of the distribution of filarial infection and its variation the chief factors of endemicity appeared to be (a) the period of effective transmission (b) suitable breeding places for the transmitting mosquito and (c) density of population Temperature and humidity play an important part in the metamorphosis of the filarial embryo in the mosquito Optimum temperature and humidity must correspond with the breeding of the mosquito and the longer the period of coincidence of these factors the higher the microfilaria rate

Transmission of Filarial infection The chief intermediate host of *W bancrofti* in nature is *Culex fatigans* ... areas a large percentage of them were ... xperimentally that high atmospheric hu ... F) were necessary for the embryo to ... With this combination of temperature and humidity the rate of development of the worm in the mosquito is very rapid During the monsoon months when both humidity and temperature are high the mosquitoes show heavy infection During this season complete development of the embryos takes seven days During the winter months the infection rate is very low and the time taken for the completion of development is usually about 18 to 20 days

Culex fatigans, Anopheles philippinensis A pallidus, A fuliginosus, A stephensi and *A ludlowi* were found to be efficient intermediate hosts of *W bancrofti* In conformity with the experimental observation, natural infection was observed in *A ludlowi A philippinensis* and *Culex fatigans*

Pathology — ... urious effects and the only indication of their ... They may however, produce grave lesions Var ... rosis may occur round the adult parasites Th ... of lymphatics and inflammatory reaction are fever Living or dead worms are frequently found in the glands

Elephantiasis may be filarial or non filarial, there may be congenital and sporadic forms of different etiology *W bancrofti* is the commonest cause of tropical or endemic elephantiasis Obstruction of lymphatic vessels and bacterial infection are both important factors in the production of this condition

The attack of lymphangitis is ushered by a rigor and fever (101 to 104°F) lasting for several days headache, vomiting rarely suppression of urine and albuminuria The affected part is tender painful and oedematous ... and may show as visible red congested streaks ... it the appearance of erysipelas After several d ... ends with profuse sweating or abscess formatio ... infiltrated and attacks may go on recurring leading to hypertrophy and elephantiasis Microfilariae may or may not be present in the blood The inflammatory process may spread to the deep lymphatics

Elephantoid fever may occur at varying intervals (weeks months or years) and in India it is popularly associated with lunar influences Onset of fever is usually quite sudden and the temperature may become normal in 24 hours or may last several days or even a month Paroxysms may occur independently of lymphangitis (due probably to inflammation of deep seated lymphatics not visible) Adenitis of lymph glands may accompany or preceed lymphangitis

Funiculitis or lymphangitis of the spermatic cord commonly occurs and filarial orchitis and hydrocoele are common conditions Chyluria results from dilatation of the lymphatic duct or some of the abdominal lymphatics communicating with those which carry chyle from the intestines Rupture of these into the mucous membrane of the urinary tract or bladder, produces chyluria which often starts quite suddenly Sometime it is preceded by pain in the back or acting sensation in the lower abdomen and thighs The attack may be accompanied by fever, and in other cases there may be retention of urine due to coagulated lymph Chylous ascites may occur Lymph scrotum varicose groin glands and filarial abscess may result

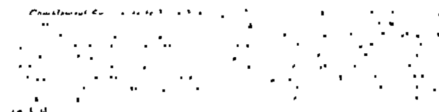
Recent work has brought out the importance of secondary infection in fatal cases of this disease. Many cases of acute septicaemia in endemic areas are due to abdominal filariasis.

Elephantiasis commonly occurs, and in 95 per cent of cases the lower extremeties are involved.

The prognosis, apart from disabilities produced, is good in elephantiasis. The condition is chronic and may last for years.

Rarer complications are filarial synovitis, resulting in fibrotic ankylosis of different joints, or even abscess formation.

Diagnosis. Blood especially that taken between 10 P.M. and 2 A.M. may show microfilariae. Adult filariae may be found either dead or alive in various localities, microfilaria may be found in chylous urine or hydrocele fluid.



A cutaneous test has been devised with 1 per cent saline extract of the *D. immitis* antigen.

Prophylaxis consists in anti-mosquito measures. The microfilaria carrier persons should be isolated so far as possible.

Microfilaria malayi. This microfilaria differs from *W. bancrofti* morphologically and biologically. Intermediate hosts are *Mansonoides annulifera*, *M. annulatus*, *Anopheles barbirostris* and *A. hyrcanus*. They are mostly night feeders. *W. malayi* is associated with elephantiasis of limbs.

Treatment for filarial infection may be dealt with under the following headings :— *Treatment*

(1) *Anaphylactoid symptoms.* The production of anaphylactic symptoms varies with individual susceptibility. Every case should be carefully investigated and treated accordingly. Recently, Goyal and Sundar Rao (1940) have demonstrated the presence of a specific allergen in cases of filariasis and they have also shown that it could be utilized successfully in the treatment of allergic type of cases.

In addition, vaccines made from the various strains of streptococci and

(2) *Filarial disease.* Lymphangitis, abscess and elephantiasis are the common manifestations of filarial infection. In a large number of cases the acute attacks are due to secondary infection. When they are caused by streptococci, high temperature sets in with a fairly high leucocyte count. When

used with good results In case of abscess formation surgical treatment is necessary

In early stages application of suspensory or pressure bandages together with treatment for filarial infection is recommended In advanced cases surgical operation for removal of the varix may be necessary

In cases of elephantiasis surgical operation for excision of hypertrophied tissue has been recommended It should be remembered however that such operations will not cure the disease Massage pressure bandages prevention of secondary infection and treatment for the same are helpful in reducing the size of the limb and checking its growth Periodical courses of mixed streptococcal and staphylococcal vaccines have been found to give good results In case of genital affection surgical treatment for the excision of elephantoid tissue is recommended

A large amount of work has been done to find a *specific drug for filarial* infection but no success has been attained so far Many drugs chiefly com pounds of arsenic antimony bismuth and
tried without success Investigations hav
of zinc lead tin and gold Various synth
tried orally and also by injection but without success

Filariasis has been treated with antimony compounds in intensive doses on experimental scale Workers have tried anthiomaline and some other com paratively newer antimony derivatives and the results are said to be encouraging

Prophylaxis of filarial infection consists chiefly in antimosquito measures and isolation of the early infected cases (carriers)

Chyluria lymphuria or haemato chyluria Blockage by adult parasites at the level of (1) the juxta aortic glands which drain the lymphatics of the kidneys or (2) the iliac (internal) glands which drain the lymphatics of the bladder results in lymph varix which ruptures on strain or trauma and leads to leakage of chyle or lymph sometimes mixed with blood The urine is clear in the morning or after rest but becomes milky after a fatty meal Cystoscopic and pyelographic examinations are helpful in locating the site and the side affected Secondary infection is very common in chyluria—culture of a catheter specimen or midstream urine shows streptococci or staphylococci

Microfilariæ are always present in the blood and urine of patients suffering from chyluria They are absent in long standing cases when the parasites are dead Sometimes they are present only in blood or only in the urine

... treatment of these conditions absolute rest is necessary Restriction

... ections of ...

um

The

Soamin subcutaneously intramuscularly or ... with 1 gr (0 06 gm) to maximum 3 gr (0 2 gm) twice weekly Total 20—25 gr (1 3 to 1 6 gm)

N A B neosalvarsan or sulfarsenol 4—6 doses

Tryparsamide, 2 gm in 10 ccm of distilled water intravenously once a week, not exceeding a total of 8 gm.

Antimony compounds Recent observation in human filariasis shows that [illegible]

Rao (1929) tried almost all the pentavalent organic compounds of antimony *e g*, urea stibamine, stibosan, neo stibosan, etc in filariasis without any effect The same is the case with other helminthic infestations *e g*, lung infections (paragonimiasis) Recently in the hands of American workers neostibosan has given good results

Anthiomaline Brown (1945) used anthiomaline intramuscularly, 3 cc every day till a total of 60 cc was given in 20 days and claimed that microfilaria disappeared from peripheral circulation for about one year Culbertson and others (1946) used various antimony preparations pentavalent and trivalent with promising results They opined that neostibosan I V was the best drug when [illegible]

varied from 0 5 mgm to 2 mgm per kilogram body weight three times a day for three to twenty two days In all instances the number of microfilarial was markedly reduced from the second day of treatment and in most cases remained low in number for about 8 9 months Evidence also points to its favourable action on the parent worms

(2) Loa Loa Filariasis

Loa Loa is a human filaria which occurs largely in West Africa mainly along the low lying coastal regions and along the course of big rivers and deltaic areas *Loa Loa* or eye worm is smaller than *W bancrofti* The embryos maintain periodicity in the blood which is exactly the reverse of *W bancrofti* that is the embryos appear in large numbers in the day time and disappear at night Mangrove fly (*Chrysops dimidiata*) is the intermediary development taking place in the thoracic muscles and fat of the body they pass [illegible]

Loa Loa migrates to the subcutaneous tissues and moves about in this situation it is frequently found under the skin of fingers back and above the sternum and has a tendency to appear in the ocular region especially the conjunctiva There is persistent eosinophilia 30 to 60 per cent Warmth attracts the worm to the surface of the body

Clinical features

The migration of the parasite produces no serious inconvenience but slight local irritation may occur There may be pricking and creeping sensations and transient oedematous swellings—(calabar swellings) about the size of a hen's egg appear in various parts of the [illegible] cause much trouble When the [illegible] considerable irritation and photop[illegible] give rise to serious consequences [illegible] atitis may sometime occur Cys[illegible]

Diagnosis

Thick blood film may show microfilaria Confirmatory evidence may be obtained by intra-dermal and complement fixation tests as in case of *W bancrofti*

Treatment—The swelling is very difficult to treat. Use of evaporating lotions relieves irritation. According to some authorities, infection may be controlled by *tartar emetic injections* or anthiomaline intravenously (3 ccm of 6 per cent solution every other day). Worms may be removed from under the conjunctiva under local anaesthesia but this does *not necessarily remove the infection*.

Other *filariae occurring in man* are *Mansonella ozzardi* (*F. ozzardi*) which occurs in the West Indies and South America, and is identical with *F. demarquayi*. The intermediary insects are midges *Culicoides furens*.

Filaria perstans occurs in the Gold Coast, Central and other parts of Africa and develops in midges *Culicoides austeni*.

(3) Dracontiasis

Dracontiasis is the invasion of the connective tissue by *Dracunculus medinensis* probably the "fiery serpents" mentioned by Moses. The adult female 30 to 120 cm long and 0.5 to 1.7 mm in diameter. It works its way and arrives at *the surface of the skin* producing a local lesion and systemic symptoms, *e.g.* urticaria, etc. If the parasite ruptures acute inflammatory symptoms appear. The disease is transmitted by some species of cyclops. When the embryos are swallowed by the cyclops they pass into the haemocoele cavity where they undergo metamorphosis. In 4 to 5 weeks the larvae mature and are ready to enter the human host.

The larvae remain in the body of the parent worm and are only freed at the time of parturition when the head of the worm is brought in contact with water or when it ruptures during extraction. In clear water the larvae remain alive for six days while in muddy water and moist earth they may live for 2 or 3 weeks. They resuscitate slowly and sometime only partially.

Transmission—The cephalic end of the female approaches the skin as the papule formed in the skin becomes vesicular. When the blister ruptures and the part comes in contact with water the head of the worm is thrust out through the opening in the skin. The uterus of the worm then prolapses through the ruptured anterior wall of the mouth and the first stage motile larvae are repeatedly discharged into water and are swallowed by the cyclops. Man becomes infected by ingesting the infected cyclops by drinking infected water. The action of gastric juice kills the cyclops and the larval forms become freed. They penetrate the wall of the duodenum or the stomach, migrate through the tissues and finally lodge in the subcutaneous tissue. It takes 10 to 14 months before the female matures in this position and is ready to discharge its larvae. The male dies after it has fertilized the female and disappears.

Clinical symptoms and pathology—*The female after maturing generally travels towards the legs and feet and sometimes into the scrotum*

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the opening out ...
of milky fluid exudes from the head

The *toxic symptoms* subside after the rupture of the vesicle and the appearance of *the head in the opening*. Following this the area round the worm becomes extremely painful and oedematous and the toxins excreted and secondary infection may lead to cellulitis. Non bacterial inflammation has been described to occur round different joints and *is responsible* for a lot of crippling. The worm may sometime die before reaching the surface and may become absorbed or calcified. The latter condition may produce synovitis, periostitis or sciatica.

Diagnosis is only possible when the worm appears at the surface of the skin or when it is found on opening an abscess or after aspirating a joint. X-rays may be useful in locating the worm. Eosinophilia about (13 per cent) may be present, but it may be absent. An intradermal test with a saline extract of the parasite is said to be positive in nearly 50 per cent of the cases.

Diagnosis

Prognosis is good. Generally only one worm is present but sometimes there may be two or more. The danger of reinfection in endemic centres is always present.

Treatment—As soon as the worm is detected the patient should be put to bed and the affected part should be rested. Most of the trouble arises because the patient uses the limb and thus inflammatory changes are favoured and secondary bacterial infection takes place. When systemic symptoms (urticaria, pruritus, nausea, dyspnoea, etc.) are marked give an intramuscular injection of 5 to 10 minims of adrenaline. The old method of opening the blister with an aseptic scissors, removing the necrotic skin and douching with cold water is still the best. By frequent cold douches the uterus is gradually forced out and empties the embryos. Until this is done the hook end of the tail assists the worm to maintain its hold in the lesion. When parturition is completed, and this takes 15 to 20 days, the worm often gets absorbed or tends to come out. The lesion should be kept covered with aseptic gauze and kept moist with sterile water while parturition is taking place. The dressing is changed 2 or 3 times a day and cold douches are given. When the worm emerges a silk thread is tied to it and it is wrapped round a small piece of bamboo or wood. Attempts should then be made to extract the worm by gentle traction, care being taken not to break it. The average period of extraction is 23 days but it may take as long as ten weeks. Extraction by incision over the worm and dissection is not recommended except when the worm lies coiled about itself. By surgical extraction the period of illness may be cut down to 11 days. The worm may be cut out in pieces through the skin at several points but care should be taken to avoid drawing the anterior end back through the tunnel.

Treatment

A number of drugs have been used to kill the parasite, e.g. intravenous injection of tartar emetic or novarsenobenzol; local injections into the worm of chloroform, cocaine, chinosol (1 in 400), perchloride of mercury (1 in 1000) have been tried. The difficulty lies in putting the needle into the body of the worm and even then it is not certain if the fluid will go into it. Injections of 1 in 10,000 acriflavin solution is preferred by some as it produces no local irritation or systemic disturbances and gives immediate relief to itching.

If cellulitis has already occurred complete rest must be enforced and hot carbolic acid (1 in 40) or lysol fomentations are freely applied. Sulphonamide derivatives such as sulphathiazole and sulphadiazine may be given in usual doses, penicillin may also be used. If the cellulitis is severe and shows a tendency to spread, incision should be made and pus should be evacuated. Abscesses formed in the breast or in the limbs should be opened and freely drained.

Treatment of cellulitis

If joints are affected surgical treatment may be necessary and in most cases removal of sterile pus by aspiration is all that is required.

During convalescence the affected limb should be used with care. Calcified worms may produce sciatica and in such cases removal of these after locating with [illegible]

[illegible] injec-
tions [illegible] tion
is relieved and as a rule a [illegible] to

clear the infection, though in some cases a longer course has to be given. Sometimes, the injections have the effect of bringing to the surface other guinea worms which happen to be in the body. Hamilton Fairley tried antimony tartrates in guinea worm infections without success, he prefers emetine injections given intravenously.

water containing infected cyclops
infection. The larvae should be
and cyclops should be destroyed
o 65°C by passing steam from a
boiler, but this treatment has to be frequently repeated and is expensive. Cyclops can also be killed by introducing potassium permanganate or quick lime in solution of 1 in 1,000.

Monthly applications of bleaching powder (3 pounds per 100 000 gallons and copper sulphate 1 pound per 200 000 gallons) kill cyclops.

Biological control by introduction of fish *Barbus puekelli* which feeds on cyclops and also on the larvae of the worm may be tried. For personal prophylaxis boiling and filtering of drinking water even through ordinary calico cloth is effective.

(4) Onchocerciasis in Man

worm' is a tropical nematode widely prevalent
in
l Kenya and Sudan. It also occurs in tropical
Am
ltitude of about 3000 feet. *O. volvulus* (F
vol
fibrous multiple tumours varying in size from
a
n found in the blood but usually microfilariae
occur
l in the regions of the body where lymphatics
converge, e.g. axilla, poplite
ntercostal
spaces. The dense mass of
female
worms. Usually there are
tumours
are present in the scalp and
are age
lymphatic enlargement of the scrotum, hydrocele and enlarged testes may be present and localised abscess may form. Acute arthritis may occur and microfilariae may be found *in the synovial fluid*. Dermatitis thickening of skin and wrinkling may be present. Lesions of the iris, cornea and choroid may occur with photophobia, impaired vision, complete opacity (pannus) and blindness.

Treatment.—Excision of tumour in early stages arrests progress of eye or skin symptoms. Intravenous injections of neostibosan sometimes arrest the progress of corneal lesions. Microfilaria may sometime disappear from the skin under intravenous injections of sodium antimony tartrate continued for four weeks. Protein shock treatment may improve ocular and skin lesions. According to some authorities atebrin *in large doses* has a definite value. Heliobrom (*dibromotannic urea*) 10 per cent in spirit applied to the skin at night relieves irritation. Drugs such as gentian violet and hexylresorcinol may be injected into the centre of the nodule to kill adult worms. Injection of 0·1 per cent plasmochin is recommended to control ocular symptoms by *killing worms in the* vicinity.

(5) Trichinosis

Trichinella spiralis the trichina worm is a very small worm parasitic in man, pigs and rats and occasionally other animals. Man ordinarily becomes infected from eating pork in which the larvae are encysted. When the cysts reach the stomach the larvae are liberated and develop *into the* adult state in the intestines. The adults live for only a short time in the intestines reproducing great numbers of living embryos which burrow through the intestinal walls and are carried to various parts of the body by the circulation and

encyst in striated muscle fibres. This life cycle may occur in any one of the susceptible hosts. The effect of trichinosis depends on the stage of infection, the number of parasites

There is no specific treatment. The general treatment is the same as of any acute infection. The oral and parenteral use of most of the ordinary anthelmintic drugs is useless and should not be employed. Absolute rest and administration of sedatives such as aspirin every or 4 hours will relieve severe muscular pains or codein may be given in one grain doses. If drugs by the mouth fail morphine may have to be given. Transfusions of whole blood and plasma may be required. Use of iron by the mouth or by injections may be required.

Treatment

7. General Considerations in Anthelmintic Drugs

Anthelmintic (from *anti* against and *helminthos* worm) are therapeutic agents used to destroy parasitic helminths in the hosts body or to remove them from the body. It is commonly applied to those drugs which expel worms from the gut but it includes remedies used against worms in the liver bladder connective tissue etc. These remedies have been commonly but inaccurately divided into vermicides (vermes caeders) and vermifuges (vermes fugare). There is however, no sharp line dividing vermicidal and vermifugal drugs as very often the same drug may have a vermicidal and a vermifugal action according to the dose in which it is given. Some drugs such as santonin have an entirely vermifugal action as the parasites are expelled alive while others like chenopodium are vermicidal. Male fern is classed as a vermicide though the tapeworms are often expelled alive. Helminths occuring in blood vessels (e.g. *Schistosoma*) or in the lymphatic vessels lymph nodes lymphatic tissues (*Wuchereria*) in the parenchyma of lungs (lung flukes) in the musculature (Trichinella larvae and Cysticerci) may be killed by specific drugs but the problem of saving the host from the effects of the products of disintegration of the dying or dead worms is yet unsolved.

Introduction

(1) Requisites of Ideal Anthelmintic

The qualifications requisite for an ideal anthelmintic are

(1) It should be safe for the patient. It should be borne in mind that anthelmintic drugs in general are not toxic specifically to the worms alone but in a greater or lesser degree to all living cells; they may even be dangerous to the host. It is therefore advisable that prior to the administration of the anthelmintic accurate diagnosis be made by microscopic examinations of the stools urine blood etc. and the patient carefully examined with regard to the condition of his heart lungs kidneys and liver so as to be sure that he can safely stand the treatment.

(2) It should be effective in removing the particular kinds of parasites for which it is given. This depends on several factors such as location and

species of parasite the choice dosage and purity of the drug used the preliminary preparation of the patient administration of a post purgative dietary measures etc In spite of every precaution there are no anthelmintic drugs which have a 100 per cent efficacy in safe doses for any species of parasites. Fortunately it is not essential to remove all the parasites as unlike bacteria or protozoa they *do not except in a few instances multiply* in the body Expulsion of the majority of worms is usually sufficient to render the infection innocuous It is well known that hookworm infection is practically universally present all over India but the incidence of parasites in certain parts is so low that no untoward effects are produced

(3) Simplicity of administration This is of little consequence in the treatment of individual cases but when treatment has to be carried out in large labour forces it is of great importance as it not only saves time and trouble but also expense

(4) *The treatment should not be unpleasant and it should have as little* after effects as possible This is of importance when treating labour forces as labourers will not take a drug with an unpleasant taste or one which produces *disagreeable effects*

(5) The cost of the drug should not be high. No expensive preparation *will succeed for use on a large scale as an anthelmintic however effective it* may be

In the past it has been taken for granted that because a remedy is active against one species of parasite it will be efficacious against others also These *parasites however belong to several widely separated zoological groups* and differ greatly in their anatomy physiology habits and habitat It is not reasonable therefore to expect that any one drug will be effective in anything like an *equal degree against such widely different organisms*

From the therapeutic point of view the anthelmintic drugs may be divided into two main groups

(1) Drugs Acting on Intestinal Helminths

It is desirable to use drugs which are absorbed as little as possible from *the gut thus ensuring their* contact with the parasites in maximum concentration and at the same time exerting a minimum effect on the host The drugs are given by the mouth and recently some have been introduced directly into the *duodenum by a duodenal tube* sometimes drugs are introduced into the rectum and colon in the form of enemata In rare cases a solution of the drug is used intravenously Hookworms roundworms (ascaris) and intestinal flukes are *fairly susceptible to these drugs* tapeworms are moderately susceptible and enterobius strongyloides trichostrongylus trichuris and others still hold out to a large extent against all efforts to dislodge them

(2) Drugs Acting on Parasites Living in the Tissues of the Body

For the extra intestinal parasites readily absorbable drugs are given which are more toxic to the parasites than to the host *These drugs may be given by* mouth but are *often* administered by subcutaneous intramuscular or intravenous injection. It is only in recent years that any headway has been made against such somatic infections and fairly effective *remedies have been discovered* for schistosomes liver flukes, etc

(3) Modes of Administration

It has already been stated that all drugs belonging to this group are toxic not only to the parasites but to the host also Certain precautions regarding diet dosage and prevention of absorption of the drug are necessary to minimise toxic effects Anthelmintic treatment consists of three stages —

Preparation of patient

(1) *The preparation of the patient* In the old days starvation of the patient and a preliminary purgative were considered essential the idea being to get the alimentary canal as empty as possible so that the drug could come into intimate contact with the parasites It has been found that starvation has a weakening effect on the patient and renders him more susceptible to the toxic action of the drugs, further absorption is increased from the empty intestines In the [illegible]

concentration as possible. Some anthelmintic drugs such as tetrachlorethylene carbon tetrachloride and oil of chenopodium are not only quite as effective when given without preliminary starvation and purging but preliminary fasting and purging considerably enhances their toxicity for the host For tapeworm infection it is necessary that the drug should come into contact with the heads of the worms otherwise the main body of the parasite is likely to break off leaving the head intact and in a few weeks the whole chain of segments is regenerated The *preliminary preparation in the form of a liquid diet consisting of milk or broth* on the previous evening and withholding of food on the day of treatment is therefore essential Even with the most careful preparation the best remedies give only about 50 per cent of cures and without preparation the hope of success is much reduced Strongyloides and trichostrongylus are also deeply imbedded in the intestinal wall and though no specific for them has yet been found the preliminary preparation in the manner mentioned above seems logical

Absorbable fats are contraindicated with most of the anthelmintics used against the intestinal parasites as their presence in the gut leads to absorption of these drugs Many of the anthelmintic drugs *e g* carbon tetrachloride thymol are soluble in alcohol and its presence in the gastro-intestinal tract is liable to increase their absorption thus producing toxic effects It is best therefore to forbid its use For remedies which have a deleterious effect upon the liver (*e g*, carbon tetrachloride) if this organ is well stocked with glycogen it is relatively resistant and therefore a rich carbohydrate diet is indicated In the case of drugs which are poisonous but very insoluble in water *e g*, thymol the amount of water consumed should be cut down to minimum to prevent their solution and absorption On the other hand with drugs which are largely absorbed and excreted by the kidneys *e g*, beta naphthol plenty of water should be given

[illegible] Some foods [illegible] Mechanical [illegible] nd the husks [illegible] diments such as mustard pepper onion garlic spices etc., were recommended in the olden days as accessories to anthelmintic treatment Although *in vitro* the anthelmintic power of drugs is enhanced by the presence of these substances their value *in vivo* is doubtful

The selection of a preliminary purgative depends on the nature of the anthelmintic to be given In the case of thymol and carbon tetrachloride oily purgatives *should be avoided because these drugs* are soluble in fats and the chances of absorption are increased Non absorbable oils such as castor oil or paraffin oil are much less dangerous but even these are not recommended In the case of drugs like chenopodium, oily purgatives can be advantageously used Chenopodium oil is readily soluble in castor oil and since it is a local irritant its dilution in non absorbable oils is advantageous in preventing it from coming in contact with the mucous membrane in concentration which will be injurious Castor oil also neutralises the paralytic action of chenopodium on the intestinal wall As a general rule, *it is preferable to give saline purgatives because they* do not increase the solubility of the drug they create an osmotic pressure and a flow into the lumen of the gut, instead of away from it and lastly they tend *to dissolve mucus and, therefore expose the parasites to the action of the* anthelmintic Magnesium sulphate or sodium sulphate or a combination of the two, in dose of one ounce of the saturated solution diluted to two or three ounces is recommended

The method of administration is determined by the drug prescribed Water soluble drugs, if they have not a nauseating taste, may be given in water Fat soluble drugs, like beta naphthol and oil of chenopodium if also water soluble and absorbable, may be given dissolved in non absorbable oils Drugs which are poisonous after absorption in large quantities and which owe their safety to the fact that they are insoluble in water, *e g*, thymol carbon tetrachloride should under no circumstances be given with fats It is always safer to avoid the use of oils entirely with male fern Carbon tetrachloride is insoluble in water and is dangerous if dissolved in oil, it emulsifies when shaken vigorously *with milk and the latter forms an excellent medium for its administration* Given in this way it becomes uniformly distributed in the stomach and the burning sensation which it usually produces is reduced Tetrachlorethylene is *conveniently administered after being shaken up with a solution of the saline* purgative in a bottle For nauseating and objectionable tasting drugs, *e g*, chenopodium, filix mas, etc, gelatine capsules are useful Hard capsules should always be used since soft gelatine capsules *do not dissolve in the upper part of* the intestine where the action is desired Soft capsules are best used in the case of worms residing in the lower portions of the gut, *e g*, enterobius, trichuris

Powdered drugs can be given in the form of powders cachets or tablets and they are often combined with substances which aid their action *e g*, santonin is combined with calomel It is better to give some drugs such as oil of chenopodium, betanaphthol male fern etc, in divided dose at intervals of half an hour to one hour as this insures a longer period of contact with the worms Besides if [illegible] withheld Division of doses is [illegible] of individuals have *to be treat*[illegible] [illegible]oride this method is contra indicated as it is liable to promote absorption

[illegible] Ryles tube are first dissolved [illegible]tian violet *solution the tube* [illegible]n in and then should be with[illegible] in contact with the gastric mucosa may set up vomiting

Anthelmintics in the form of enemata are given for parasites residing in *the large intestines and many* substances have been recommended for this purpose,

e g, sodium chloride, quassia turpentine, hexylresorcinol, etc The enema *should be injected as high up into the colon as possible* because often the parasites such as oxyuris are situated in the cæcum and in the neighbourhood of ileocæcal valve It should be preceded by a purgative and liquid diet the night before and a preliminary washing out of the colon with soap and hot water on the morning of the treatment Sometimes an anthelmintic given by the mouth is effective in this class of infection

Parenteral routes

For parasites residing in the tissues intravenous injections of drugs such as tartar emetic, emetine etc are desirable in fasciolopsiasis emetine has also

infestations drugs may be administered by inhalation Local application or ethyl chloride spray or carbon-dioxide snow or radio therapy is done in creeping eruptions

Use of post purgative

(2) *Expulsion of the worms and the toxic drugs* A postpurgative may have to be used in the case of some of the anthelmintics as they merely stupefy or paralyse the worms or possibly merely irritate them and if they are not quickly swept out in this condition they may revive and obtain a fresh hold A brisk purgative in these cases quickly washes them out from the intestines while they are still under the influence of the drug Some purgatives have an irritating effect on the parasites and the increase of peristaltic movements also helps in removing the unattached parasites Some anthelmintics have a purgative action of their
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The time at which a post purgative is given is determined by the location *e g* for hookworms and ascaris situated in the upper portion of the gut it may be given simultaneously with the anthelmintic (which is an advantage especially in carrying out mass treatments) or very soon after For tapeworms situated lower down the post purgative is sometimes given one hour after for enterobius and trichuris an interval of two hours may be necessary It is often advisable to give another purgative on the second day of treatment as it may eliminate some of the worms which have succeeded in establishing themselves temporarily in an unfavourable situation lower down in the intestine

Repetition of courses of treatment especially in case of the intestinal parasites liver flukes etc should never be made in less than one to two weeks to allow sufficient time for the repair of any damage to the host caused by the first course Besides it is seldom possible to be sure that the anthelmintic has failed in less than a week or even longer In the case of treatment of tape worm infection even when failure is established by unsuccessful search for the head it is advisable to wait until the parasites have had time to grow again since the weight of the paralysed or killed worm may draw the head away or may bring it into a position where it is exposed to action of the drug later on

(4) Criteria of Cure

Disappearance of eggs or embryos in the fæces is the usual criterion of cure and is applicable to all intestinal and hepatic flukes and nematode infections except oxyuris Eggs deposited in the gut prior to treatment may possibly

appear in the stool for a few days afterwards Tetrachlorethylene carbon tetrachloride and some other anthelmintics also have a tendency to inhibit production of eggs for a time, without necessarily killing or expelling worms, in the case of tetrachlorethylene and carbon tetrachloride this inhibition may be exerted for as long as ten days A re examination of the stool should be carried out after that period though a positive examination between the third and twelfth day of treatment conclusively indicates failure Delayed cures are also effected in the case of hookworm and possibly some of the other parasites, the eggs cease to appear and the worms are expelled a few weeks after the administration of the anthelmintic This is due probably to the parasites being swept into unfavourable positions in the intestine where they persist for some time but eventually lose their hold and are expelled It should also be borne in mind that reappearance of eggs two to three weeks after treatment, while it shows that a complete cure has not been effected, does not mean that the anthelmintic has proved entirely useless In the case of hookworms intestinal anthelmintics often cannot reach the young worms which are hidden in the folds of the mucous membrane or between the villi or which have not reached the alimentary tract The young parasites and even some of the old ones (*e g*, strongyloides) may bury themselves in the mucosa and may thus be out of reach of the drug

In the case of enterobius, the search for eggs cannot be relied upon as a criterion of cure, since eggs are not consistently present in the stools but only when female worms become crushed or disintegrated The entire stools should be searched for the adult living worms or anal swabs examined for eggs Besides reinfection not infrequently occurs and enterobius found in the stools a few weeks after treatment does not necessarily mean that the anthelmintic was ineffective In strongyloidiasis the disappearance of larvae from the fæcal smear is not a sure criterion of cure Repeated cultures of stools as done for growing hookworm larvae, are to be examined and when these are negative cure is presumed In the case of tapeworm the criterion of cure depends on the species involved The dwarf tapeworm of man (hymenolepsis) can be detected by searching for eggs but it may be several weeks after treatment that the eggs reappear This is due to the fact that even though the worms are not expelled the body is broken off just behind the head and it takes time for the segments to re form In the majority of tapeworm infections much reliance cannot be placed on searching for eggs, segments may be found in the stool but this takes time In the case of the tæniæ also the body breaks off and it requires two to three months before the parasite matures and segments reappear

... from the

can be determined at once by examining them under the microscope or by the hatching test, this is carried out by washing them and putting them into water when the majority of viable eggs hatch out in a few hours and the liberated embryos can be seen swimming about In the case of *Wuchereria* infections it is not known how long the embryos circulate in the blood if the parent worms are dead, the criterion of cure has, therefore to be worked out

(5) Experimental Investigation of Anthelmintic drugs

The experimental work is difficult owing to the impossibility of using artificially infected animals on a massive scale as can be done with protozoal diseases The effect of anthelmintic drugs can be tested on parasites *in vitro*, but these parasites are difficult to obtain and to

keep alive Sollmann (1918) employed earthworms for testing the action of anthelmintic drugs *in vitro* and found that the drugs which are non toxic to these worms are not likely to be active, while drugs which are lethal to them have possibilities of effective anthelmintic action In some cases the toxicity to the earthworm runs parallel with their toxicity ... been evolved ... volumes of ... n one vessel ... eme restless ness or spastic contractions indicate irritation—possibly vermifugal activity The time of death is noted and the results are compared with a similar series made with a standard preparation Aspidium, chenopodium santonin, spigelia, etc., can all be standardised by this method The use of common earth worms for *in vitro* experiments is open to obvious objection as they and helminths are wide apart in the Zoological scale A more rational step would be to collect parasites, human or animal post mortem

In vitro tests are however, merely a preliminary step and must be followed by *in vivo* tests. In most cases dogs respond to anthelmintic drugs in much the same way as human beings though perhaps they are more resistant, they are, therefore, particularly suited for anthelmintic experimentation. As a rule with most of drugs known, a dog weighing 20 kilogrammes can be given the same dose as an average adult human being but this may not be so in case of all drugs The worms expelled by the drug are carefully counted and the re[illegible] tion [illegible] is first [illegible] carefu[illegible] efficacy is administered, and the worms eliminated are compared with those expelled by the experimental drug All these worm count methods are very laborious and they are [illegible] of the drug in removing worms

In vitro tests

Another method of determining the efficacy of anthelmintic medication is by making differential egg-counts before and after the treatment In the case of necators for example the number of eggs produced by a female per day is fairly well known and the number of worms harboured can be roughly estimated by determining the average number of eggs per gram of fæces for a period of not less than three days Such determinations made before the treatment and then a week or ten days after the treatment enable us to know the relative number of female worms eliminated In most infections the number of males and females is roughly about equal

Correlation between chemical composition and anthelmintic action of drugs The study of the chemical constitution of the active principles isolated from drugs has led to the synthetic production of important compounds with marked physiological properties [illegible]

The study of the relationship betw[illegible] action of compounds was first taken [illegible] work was interrupted by the War [illegible] large number of anthelmintic drugs [illegible] drugs with certain of their chemical c[illegible] brought to light in connection with the [illegible]

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Correlation between chemical composition and anthelmintic action of drugs The study of the chemical const tution of the active principles isolated from drugs has led to the synthetic product on of important compounds with marked physiolog cal properties

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The study of the relationship between the chemical constitution and the anthelmintic act on of compounds was first taken up by Hall and Meyer Widgor (1917 18) but their work was interrupted by the War Ca us and Mhaskar made an elaborate study of a large number of anthelmintic drugs and attempted to correlate the efficiency of certain drugs with certain of their chemical constituents Some very remarkable facts have been brought to light in connection with the anthelmintic action and toxic effects of these drugs —

(1) Hydrogenation of benzene lowers the toxicity towards the parasites but raises the toxicity towards the host as is the case with menthol

(2) *Total destruction of the benzenoid structure leads to the formation of* non anthelmintic toxic compounds

(3) Esterification of the phenolic hydroxyl group leads to the format on of non anthelmintic non toxic compounds *e g*, thymotal

(4) The mere presence of the phenolic hydroxyl group does not always confer *anthelmintic properties e g* iso *amyl* phenol or iso butyl phenol which contain it are both inactive

(5) The active anthelmintic principles in oil of chenopodium (paracymene, phellandrene ascaridol) and thymol contain free phenolic hydroxyl to which are attributed their anthelmintic properties

(6) Methyl alkyl appears to intensify the anthelmintic action of phenolic hydroxyl, *e g* methyl salicylate has marked anthelmintic properties while other salicylic acid compounds such as aspirin and salol are inert

(7) Neither alcohol nor aldehyde groups have any anthelmintic properties
(8) The anthelmintic activity of carbon compounds appears to be correlated with the chlorine content

It will be seen, therefore that in the majority of cases the relation between chemical constitution and their phys ological action is not very clear Change in chemical composi*tion completely changes the physical properties of compounds Their* volatility solubility osmotic properties ionisation etc undergo a complete change and so their absorption into the system and the physiological effects produced are also modified In the present state of our knowledge of the changes going on inside the body of a living cell it is impossible to speculate further

8 Drugs Used Against Helminths

The following is a list of the more common present day chemotherapeutic [illegible] ants (the latter are marked by asterisks) [illegible] chemical *nature to which recently*

I INORGANIC

- *Calomel
- Carbon dioxide snow
- Colloidal antimony
- *Ferrous carbonate (in Blaud s pills)
- *Magnesium sulphate
- **Sodium sulphate*

II ORGANIC

1 Hydrocarbons
   - *Mineral oils

2 Aliphatic halogenated hydrocarbons
   - Carbon tetrachloride
   - Chloroform
   - Ethyl chloride
   - Tetrachlorethylene

3 *Phenols*
   - B naphthol
   - Hexylresorcinol
   - Neoantimosan
   - Thymol

4 Terpenes
   - Ascaridol

5 Triamino triphenyl 1 ethane
Gentian violet

6 Organic acids their salts and esters
Antimony and potassium tartrate (tartar emetic)
*Calcium gluconate
*Calcium lactate
*Iron and ammonium citrate
Sodium antimonyl tartrate

7 Piperazine derivatives (Hetrazan)

8 Alkaloids
Arecoline (in areca or betel nut)
Emetine hydrochloride
Margosine
Pelletierine
Pyrethrins

9 Enzymes
Papain
Ficin (in leche de higueron)

10 Semi refined or unrefined plant products
Areca or betel nut
Aspidium oleresin
*Castor oil
Cocoanut
Corsican moss (helmintocorton)
Garlic
Granatum (pomegranate)
Kamala
Kousso
Leche de higueron
Oleum chenopodii
Oleum meliae (azedarach)
Onion
Papaya
Pepo (pumpkin seed)
Pyrethrum
Quassia

(1) Male Fern and Allied Drugs

Male fern, Kousso and Kamala are the three important drugs of this group Though derived from different sources they are intimately related to each other from a chemical as well as from a pharmacological point of view The active principles in all are chemically allied bodies, *i e*, derivatives of phloroglucin

(a) Aspidium (Male Fern)

Synonyms —Stipides aspidii Radix Filicis Maris Sweet brake

Male fern

This is one of the oldest anthelmintic drugs known and was used by the ancient physicians Pliny and Galen *Aspidium filix* - known varieties of ferns which are re Pharmacopœias They both contain the san quantities of the rhizome Several other growing in Europe and *A anthelminticum* principles and properties The rhizome an (Fam Polypodiaceæ) are chiefly used

Chemical composition

The chemical constituents of the rhizome are unstable bodies and undergo chemical changes even in the dry rhizome The active principles are a number of non nitrogenous substances the more important of which are as follows —*filmaron* 5 per cent *filicic acid* 2 to 4 per cent and smaller quantities of aspidin aspidinol and filicic acid In addition there are tannic acid 10 per cent inactive filicic anhydride (filicin) produced in old specimens by transformation of filicic acid 19 to 31 per cent a green fixed oil 6 to 7 per

cent, a volatile oil 0.02 to 0.04 per cent, an uncrystallisable sugar, 11 per cent, resin, starch, and wax

[illegible] ... and soluble ... chloroform ...

Filicic acid or *filicin* occurs in two forms (1) a *crystalline inactive* form and (2) an amorphous form which is said to be mainly responsible for the therapeutic activity of the drug The crystalline form is the lactone of the active amorphous form and the latter *readily* changes into the former This is the reason why the rhizome and its preparations deteriorate so quickly

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Internally filicic acid has a strongly irritant action on the gastro intestinal tract and may produce vomiting and blood stained diarrhœa and in excessive doses collapse and [illegible] ... reflex uterine contrac [illegible] ... ffected even [illegible] ... nd cirrhosis [illegible] ... kened. The spinal cord *is stimulated at first producing twitchings and with large doses convulsions* occur, later ascending paralysis of the spinal cord sets in and death occurs from failure of the respiratory centre *Small amounts of the active principles are absorbed from the* gut and filicic acid and its decomposition products are excreted by the kidneys

The fresh ethereal extract is usually administered in dosage of 10 to 30 minims every half an hour in capsules till the full dose is given, a grain of calomel may be added to each capsule I [illegible] ... with the yolk of an egg or some flavoring [illegible] conceal its nauseating taste [illegible] said to enhance its efficacy [illegible] adult and 7½ to 15 grains ([illegible] doses 10 to 30 minutes apart, the last dose being followed in ½ to 1 hour by a full dose of magnesium sulphate Pills coated with keratin are preferred by some Clayton Lane and Low recommend the following method of administration of the drug liquid diet for two days, calomel or a saline purge in the after-*noon of the second day*, a *cup of black coffee the next morning* (third day), then one capsule containing 30 minims of the liquid extract at intervals of ½ hour till three such are given A drachm of brandy with 15 *minims* (1 0 *ccm*) of chloroform may be given with the first dose, to prevent vomiting A saline aperient (Epsom salts, Carlsbad salts or sodium sulphate) is given two hours *after the last dose*, to wash out the parasites and the drug

In treating cases with the extract of *male fern, three things are essential*, (1) The alimentary canal should be properly prepared for the reception of the drug The head of the parasite lies imbedded in the intestinal mucosa between the villi, and unless the bowel is empty the drug does not reach it (2) The extract, if used, should be fresh This is important as the power of the extract to retain its potency *is uncertain* The active principles of filix mas are easily destroyed and it has been noticed by several observers that the dried rhizome of the male fern gradually loses its *activity on keeping* The extract should be made from specimens that have not been kept for more than a year (3) The post

purgative given should be a powerful one, so that the head of the worm loses its hold and is expelled from the intestine

All stools passed for 24 hours after treatment should be saved and passed through a fine sieve to search for the presence of the scolex or the head If the head is not found cure has probably not been effected and another course of treatment will be necessary If the major portion of the worm has not been expelled treatment might be repeated after an interval of 10 to 15 days following the first course as the drug undoubtedly has a cumulative toxic effect The [illegible] one worm should be borne in mind and [illegible] ng together the expelled segments Some [illegible] means of duodenal tube, thus preventing the chance of vomiting out the drug

Anthelmintic effects

The older physicians used this drug against all forms of helminthic infections but recent work has shown that it has little value against ascaris, hookworms and other nematodes Against whipworms (trichuris) a small dose of the extract (1½ drachm) daily 2 to 3 days in succession and repeated after an interval of 10 days is effective It is useless in schistosomiasis, somatic tæniasis etc., although the drug is said to have some effect against liver flukes On the cestodes the drug has almost a specific effect though failures are not uncommon The failures recorded are mostly due to the poor quality of the drug obtained from the market and the careless preparation of the patient Rarely, the parasites themselves show extraordinary resistance to the drug and cannot be expelled even after 5 or 6 treatments

In Europe and America, *filix mas* is commonly used against *Taenia* or *Diphyllobothrium* If the patients are properly prepared according to Lane and Low s method, 50 per cent of cases of *Taenia saginata* infections are cured with a single treatment It acts on *Hymenolepis nana* as well as the large tænias, but as the former are small and are embedded in the mucus it is difficult for the drug to reach them The rarer tapeworms of man *e g*, *Dipylidium caninum*, *Hymenolepis diminuta* and *Bertiella studeri* which are not normal human parasites are more easily expelled than the species which have adapted them selves to the human host

Signs and symptoms of poisoning

Male fern was formerly [illegible] experience has shown that it [illegible] its use. Toxic doses vary w[illegible] [illegible] debility, old age and [illegible] e of fatty substances [illegible] to occur after 2 to [illegible] soning has occurred after 1 drachm (4 gm) given in a day More than 2 drachms should never be given in 24 hours

The chief symptoms in these cases are headache, vertigo and bilirubinæmia, slight jaundice frequently occurs In moderately severe doses the symptoms are those of gastro-enteritis *e g*, vomiting abdominal pain blood stained diarrhœa, headache, dizziness, shortness of breath, dimness of vision or yellow

[illegible]

he loses consciousness, respiration becomes slow and shallow, the pulse weak

met with on the market is often adulterated with ferruginous sand, red brick dust, ferric oxide, dyed starch, etc.

The drug irritates the gastro-intestinal tract and even in therapeutic doses produces considerable nausea and *increase of peristaltic movements of the gut* It has thus a purgative action Large doses produce gastro intestinal irritation and set up vomiting and violent purging

The chief advantage of this drug appears to be that it can be safely given without *any preliminary* preparation of the patient, no post purgative is necessary It is much less efficient against tapeworm than male fern It is useless against hookworm, ascaris and whipworm It is a mild drug and is *only indicated in children and debilitated* individuals in whom extract of filix mas is not advisable

(d) Other Anthelmintics

POMEGRANATE OR GRANATUM

The bark of the pomegranate tree, *Punica granatum* Linn (N O Lythraceæ), has been employed as an anthelmintic in India Both the root bark and the stem bark have been used but root bark is preferable inasmuch as the alkaloidal content is greater than that of the stem bark.

The active principles of the bark are 4 alkaloids *Pelletierine* or *punicine*, the most important of the group is a colourless volatile liquid which turns dark on exposure and

pelletierine
The bark a
the alkaloid
alkaloids are
anthelmintic

... local irritant action and even in ... y are absorbed from the ... They act on the nervous ... and dimness of vision ... paralysis

... perature, are killed in about 10 minutes if 0·01 per cent

The fresh bark is said to be a fairly good anthelmintic against tapeworms The bark ... of the large quantities of tannic acid present ... *shows that it is also uncertain* ... doses of 2 to 8 grains (0·12 to ... arked toxic effects The soluble salts are absorbed ... is favoured by alcohol, and for this reason fluid extract is not such a good tæniafuge as the decoction or powdered bark If the preliminary preparation of the patient by dieting and *purging is carefully attended* to in the same way as with aspidium, pelletierine tannate will seldom fail to produce an efficient *vermicidal action* After liquid diet for two days and a strong preliminary saline purgative the night before treatment, pelletierine is given in the morning in sweetened water followed by a brisk saline cathartic half an hour later The patient should stay in bed after taking the medicine as dizziness is always experienced *The worms are expelled* 2 to 4 hours later This drug ranks next only to filix mas as a tæniacide, and is specially recommended against *infestations* with *Taenia solium* Against *Hymenolepis nana* it is not effective

Large doses of the decoction or the alkaloids produce headache, *dizziness, dim vision* nausea, vomiting, diarrhœa, weakness of the limbs followed by paralysis Drowsiness and coma may supervene *Serious disturbances* in the eyeball such as dilatation of the pupil, ... may occasionally occur

Treatment is largely symptomatic rapid emptying of the bowels administration of ... are important If the patient ... is indicated ... Tannic acid

Treatment of poisoning

The dried powdered bark is given in doses of 20 to 40 grains (1 3 to 2 0 gm) *Preparations*

Granati (U S P X) is prepared by exhausting the powdered bark with 37 per cent alcohol and 10 per cent glycerine Each ccm represents 1 0 gm of the drug

Pelletierine (mixture of the alkaloids) dose 2 to 6 grains *Ext Granati Liq* dose 30 to 120 minims *Pelletierine sulphate* dose 2 to 3 grains *Pelletierine tannate* (B P) is a yellow amorphous powder dose 2 to 8 grains *Pelletierine hydrobromide* is a brownish viscid liquid dose 2 to 8 minims

ARECA NUT Synonyms —are ... *catechu* belonging to the family Pal... China as an anthelmintic both for ... it was included in the British Pharr... on its anthelmintic value

Several alkaloids have been isolated from the seeds which are all chemically related to each other These are *arecoline* and *arecaine* which occur in the same proportions (0 1 per cent) *arecaidine* and *guvacine* occur only in traces *Arecoline* a colourless oily liquid is physiologically active the other three are probably inactive To it the anthelmintic and sialogogue properties are mainly to be attributed There is also an essential oil (which contains laurin and myristin) several sugars iron magnesium and other salts *Chemical composition*

Arecoline base is not soluble in water and is not readily absorbed the soluble salts ... *Pharmacological action of arecoline*

salts are rapidly paralysed

Areca nut is not an effective drug against nematodes and its efficacy against tapeworms and flukes is doubtful The powdered nut in doses of 1 to 3 drachms (4 to 12 gm) is given in syrup It has undoubtedly an irritant action on the gut and produces purgation but it does not expel worms Arecoline salts are given by the mouth in man in doses of 1/15 to 1/10 grain (4 to 6 mgm) or subcutaneously ¼ of the amount One to 2 grains are given to cattle to relieve colic *Anthelmintic uses*

Arecoline in pure condition is a toxic drug As it is readily absorbed from the gastro intestinal tract it is considered dangerous for use as a tæniacide Arecoline poisoning however might occur when large doses of the powdered nuts are administered The symptoms resemble those of fungus poisoning (muscarine) and consist of vomiting diarrhœa colicky pains marked salivation laboured breathing tremors convulsions coma and death If toxic symptoms supervene rapid evacuation of the bowels and administration of cardiac and respiratory stimulants are indicated *Toxic effects*

Dry and fresh powdered seeds dose 1 to 3 drachms (4 to 12 gm) *Preparation*

C pepo contains 40 per cent of a fixed oil and 30 per cent of starch a soft bitter acrid resin which is said to be the active constituent a volatile oil and 30 per cent of starch *Chemical composition*

sugars and proteins *C maxima* contains 30 per cent of a *fixed oil* and an acid resin which was supposed to be responsible for the anthelmintic activity of the seeds but later proved to be useless *Ascaris, Taenia saginata* and *Diphyllobothrium latum* are said to be irritated and dislodged by the husks and paralysed by the oil and resin *Taenia solium* and *Hymenolepis nana* are apparently more resistant

The seeds administered should be fresh, certainly not more than a month old Two to four ounces are administered crushed or beaten into a paste with water and finely divided sugar the whole being made up to one pint Sometimes a little milk is added The usual preparatory dietetic measures are carried out and a saline purgative is given the night before and again early the following morning A very light breakfast is taken and two

produced even after large doses

Cucurbita semina praeparata (B P) Dose 1 to 2 ounces (30 to 60 gm) or more

Cocoanut The flesh and milk of the cocoanut, the fruit of a palm *Cocos nucifera* are said to have anthelmintic properties and to be specially effective against tapeworms They have been largely used in India and other Eastern countries When ingested in large quantities the milk and the meat have a purgative action and are said to expel not only the worm but its head also This however, is doubtful The patient usually fasts for 24 hours drinks the milk and eats the meat of one whole nut, 2 to 3 hours later a purgative is given

3 to 4 grains (0 2 to 0 25 gm)

(2) Carbon Derivatives

This series of compounds is composed mainly of carbon and halogens It was first suggested that anthelmintic activity is correlated with the chlorine content and since chloroform shows a considerable anthelmintic efficacy against

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CCl_4)
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Large quantities can, therefore, be introduced into the alimentary canal without untoward effects

Cases are however, on record where alarming symptoms develop from therapeutic doses either due to idiosyncracy or weak condition of the patient associated with a diseased liver Other compounds related to carbon tetrachloride have also been tried Ethylene dichloride or dichlorethylene ($C_2H_2Cl_2$) has been shown to be an effective anthelmintic against hookworms but it is distinctly weaker than chloroform and carbon tetrachloride *tetrachlor ethylene* (C_2Cl_4) is as effective against hookworms as carbon tetrachloride Recent work by Maplestone and Chopra (1933) on the toxicity of tetra-chlorethylene shows that in comparison with carbon tetrachloride its toxicity is very low and use of alcohol does not seem to be a contraindication All these advantages make it the drug of choice

Carbon trichloride or hexachlorethane (C_2Cl_6) is another of these compounds which has been tested but found ineffective It is difficult to say which are the factors responsible for the anthelmintic properties of these compounds The chlorine content or chlorine

concentration has been suggested as the explanation but a close study of the properties of these compounds seems to point to the physical factor of solubility

(a) Tetrachlorethylene

Tetrachlorethylene

It is also known as perchlorethylene or carbon dichloride It is an unsaturated chlorinated aliphatic hydrocarbon having the formula, C_2Cl_4 It is a heavy liquid, having a specific gravity of 1 6 boiling point varying between 110°-120°C and chlorine content of 85 5 per cent It is very insoluble in water (1 in 10 000 or less) The drug is fairly stable in all climatic conditions, but it should be kept away from the air in well stoppered amber bottles

Pharmacological action

It is non irritating and does not produce any local effect on the mucous membrane Absorption by the [illegible] and rabbits show signs of narcosis when g[illegible] weight. Cats and puppies behave similarly [illegible] tolerate an enormous dose (10 ccm per kilo [illegible] intoxication Lamson and [illegible]

When dogs are anæsthetised with excessive amounts of tetrachlorethylene or when it [illegible]

pressure is practically negligible

Toxicity varies in different animals. Doses of 5 ccm per kilo body weight kill rabbits in 10—20 hours. Mice can stand doses of 4—5 ccm per kilo for nearly 10 hours before death ensues In cats doses varying from 5—10 ccm become fatal in 6—36 hours In dogs death occurs with doses varying from 10—25 ccm and doses below that are generally [illegible]

As an anthelmintic

The efficacy of tetrachlorethylene as an anthelmintic as in cases of other related compounds depends upon the chlorine content The efficacy is said to be increased with the amount of available chlorine From this point of view and also because of its being very sparingly soluble in water the chances of absorption from the intestine are decreased It has therefore been used in the treatment of human ankylostomiasis The drug was found to be ineffective in human ascariasis For trichuris infection tetrachlorethylene is considered to be superior to oil of chenopodium A combined treatment 1.8 ccm tetrachlorethylene and 0.6 ccm oil of chenopodium removed 94 per cent necators and 48 per cent ankylostomes according to some workers

[illegible]

to be [illegible]
on a[illegible]
doses [illegible] great advantage, especially when dealing with a large labour force is the fact that alcohol does not increase its toxicity so much The cure rate with tetrachlorethylene is greater than with tetrachloride as the dose given is larger (4 ccm) than the latter

Administration and dosage

No very special preparation is necessary before the treatment is started The patient should be advised to take a light diet the evening prior to treatment

and no breakfast is allowed on the day of treatment The drug is given shaken up in two ounces of magnesium sulphate solution and the full dose for an adult is 3 to 4 ccm When combined with oil of chenopodium the ratio should be 3 to 1 *i e* with 3 ccm of tetrachlorethylene 1 ccm of oil of chenopodium Patients under sixteen years of age should receive a reduced dose

The actual details of treatment recommended are as follows —

Two ounces of saturated magnesium sulphate solution are placed in a flask or bottle of three or four ounces capacity and four ccm of *tetrachlorethylene and one ccm of oil* [illegible] The flask is corked and shaken until the drugs are [illegible] n the finest possible droplets the dose is then given [illegible] ie drugs have time to coalesce into larger drops and [illegible] the mixture is left standing This method of shaking was adopted in the first place because it was stated that it was dangerous to give tetrachloride unless it was in finely divided droplets and the same method has been continued with tetrachlorethylene because it is considered that the even diffusion of the drug throughout the draught gives it a much better chance of coming into contact with all the worms on the gut wall and is therefore more efficient than if given as an undivided globule of one drachm

The relative toxicity of carbon tetrachloride and tetrachlorethylene on experimental animals has been fully investigated the use of the latter in human ankylostomiasis has been advocated because of its comparative safety There has so far been no report of deaths with this drug and this is correlated with its low rate of absorption Clinical observations however, point to the fact that the drug is absorbed to some extent from human intestine but not in amounts sufficient to produce damage of the kidney or liver cells In one series only one case of grave intoxication in a total of 1 500 treatments was reported and in this case there were signs of giddiness which developed into unconsciousness with twitchings of the whole body Varying symptoms of giddiness vomiting or drowsiness in 8 out of 38 cases treated with tetrachlorethylene alone and in 26 out of 37 cases treated with a combination of tetrachlorethylene and oil of chenopodium were reported in another series

It seems that tetrachlorethylene would be a very safe drug to employ as an anthelmintic and the danger of toxic symptoms can be avoided if alcohol and fatty substances are withheld during treatment

A combination of tetrachlorethylene and chenopodium has been used in the treatment of hook worms but seems to be little better than the use of tetrachlorethylene alone In the case of mixed infections however viz hookworm and ascaris this combination is of advantage

[illegible] (C Cl) is the drug of choice in hookworm infection [illegible] s entirely replaced carbon tetrachloride because [illegible] orbed only in a very small degree causing dizziness It is contraindicated in presence of round worms and also in cases of alcoholism gastro enteritis and concurrent administration of arsenicals

The most convenient form for administration is in soft gelatine capsules each containing 0 5 ccm (8 min) For mass treatment it may be given in a saturated solution of magnesium sulphate thoroughly shaken up before swallowing In children it may be given in a teaspoonful of sugar

The adult dose is 3 to 4 ccm (45 to 60 min) for children 0 2 ccm are given for every year of age up to 12 years of age The following routine is prescribed

24 hours before treatment The
irgative (magnesium sulphate or

(2) Following morning give tetrachlorethylene on empty stomach with a little water One hour after, give a brisk saline purgative

(3) The patient should lie in bed and rest till bowels have acted freely Allow plenty of fuit juice and sugar No fatty food or alcoholic drink for 24 hours

(g) Carbon tetrachloride

Carbon tetrachloride was discovered as long ago as 1849 It is chemically related to chloroform and this led to its trial as a general anæsthetic, but it was later on discarded Hall found that it removed 100 per cent of hookworms in dogs and recommended its trial in human beings The drug is well tolerated in such doses as 4 to 6 ccm, the only symptoms noticeable occasionally being dizziness, abdominal distress and vomiting Further work has demonstrated beyond doubt the great efficacy of this drug in the treatment of hookworm infestations in man The drug is toxic and has now been replaced by tetrachlorethylene

Chemistry and properties

Carbon tetrachloride is prepared from carbon bisulphide by direct chlorination in the

with chloroform, alcohol and other organic solvents such as petroleum, benzene, ether, fixed oils and essential oils When shaken with milk it forms a good emulsion and this especially skimmed milk, forms a good medium for its administration

Impurities

Carbon tetrachloride often contains carbon bisulphide as an impurity also traces of phosgene (carbonyl chloride) may occur It is believed by some that these impurities, especially carbon bisulphide, greatly increase its toxicity Strict standards of purity have, therefore been recommended and a number of brands of the purified drug are on the market for medicinal use

Pharmacological action

Carbon tetrachloride is a general protoplasmic poison *Paramoecium caudatum* and free living *amoebae* are instantly killed in 1 in 3 000 dilution, movements of chilomastix cease in 1 in 4 000 dilution.

When applied to the skin carbon tetrachloride is a local irritant, specially when its evaporation is prevented On mucous membranes it produces preliminary irritation followed by anæsthesia When given by the mouth it has a burning taste there is a feeling of warmth in the stomach due to mild irritation of the mucous membrane Reflex stimulation produces increased peristaltic movements of the stomach and intestine and 1 to 2 hours after a large dose a stool may be passed The drug passes through the stomach unchanged That a certain amount is absorbed is evident from the fact that such symptoms as dizziness and sleepiness appear soon after ingestion Absorption occurs through the lymphatics, especially when fatty substances are present in the gut By this route the drug goes straight to
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feeling in the epigastrium, followed by diarrhœa When excessive absorption occurs or larger doses are given there is stupor, dilatation of the *pupils and irregularity of pulse*, jaundice may be produced and rarely pain in the lumbar region, hæmaturia and albuminuria Death may occur from collapse and extensive lesions in the liver and the kidneys have

to toxic effects

If symptoms of poisoning occur a brisk purgative should be administered If liver damage *has occurred only symptomatic* treatment is indicated If muscular irritability is present calcium might be useful in view of the fact that there is marked calcium deficiency in the blood following bilirubinæmia Beathie et al have successfully treated a case of acute carbon tetrachloride poisoning by the administration of methionine It is thought that the cause of liver disturbance induced by carbon tetrachloride is abnormal metabolism of *methionine and related compounds*

There is a good deal of controversy regarding the toxic effects produced by carbon

and necessary precautions are taken, carbon tetrachloride is a safe drug only more expensive but is liable to produce toxic symptoms more frequently Deaths have also been *recorded after thymol administration for helminthiasis*

The drug should be pure and the dose should not exceed 3 0 ccm The whole dose should be given at one
by a saline purgative
and those, having a lo
Under no circumstance
liver co-exists or when there is advanced kidney disease A diet rich in carbohydrates, proteins and calcium is beneficial It is better to administer *the drug three hours after* a moderate meal Some recommend milk or calcium lactate for several days before taking carbon tetrachloride Preliminary starvation is dangerous *A treatment with carbon tetra chloride* should not be given for several days after chloroform anæsthesia and *it should be* given to alcoholic subjects with caution Idiosyncracy to carbon tetrachloride may exist *and small doses may produce very marked* toxic symptoms

Carbon tetrachloride can be given to malaria and kala azar patients, preferably during the afebrile period *It is well tolerated by pregnant women and children* When heavy ascaris infections are present, it should not be given alone but in combination with oil of chenopodium

A combination of carbon terachloride and oil of chenopodium is more effective than
The reason is not far to seek Carbon tetrachloride itself is
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tively
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each
tetra-
ment

Different proportions of these two drugs have been combined by various workers
tetrachloride with 1 ccm of oil of chenopodium or
ut that the proportion of the two drugs should
Chopra and Chandler (1928) recommend for
re ascaris is abundant, 2 ccm of carbon tetra-
, when ankylostomes are less numerous than
10 to 20 min of chenopodium are preferable
chenopodium in proportion of 3 parts to one
part is considered a safe and efficient anthelmintic against *T. saginata,* Daubney and

Carman, in a series of thirty patients had a cure rate of 97 per cent in what they described as light infections Maplestone and Mukerji, however, consider that carbon tetrachloride by itself, given in a single dose, is as effective as the mixture

Oil of *chenopodium and carbon tetrachloride* are readily miscible but the latter drug is more volatile and if the mixture is old the *proportions will change* It is advisable to prepare it fresh The disadvantage of this combination is that it is extremely obnoxious to take Chenopodium can be given separately in a capsule, followed by carbon tetrachloride in water, salt or milk either immediately or one or two hours after When mass treatment is given the mixture is more convenient

PREPARATIONS

Preparations

Carbon tetrachloride (U S P X) Synonym—Tetrachlorethane Commercial name—Necatorine Dose 60 min (3 0 ccm) as anthelmintic for adults

Children of *one* year should be given 10 min for a child of 10 years 30 min and a youth of 16 years 40 min Milk is the best vehicle for administration Capsules of carbon tetrachloride are available containing 20 min in each (P D & Co) capsules of 0 3 ccm, 1 ccm and 3 ccm are also marketed

(c) Other Carbon Derivatives

It has already been [illegible]
mes [illegible]
seri [illegible]
[illegible]

[illegible] view

Chloroform

Choroform—Chloroform is a well kno [illegible]
rarely internally [illegible]
minims but as a [illegible]
administered in [illegible]
tract is not mark [illegible]

Anthelmintic effects

As an anthelmintic chloroform has been used either alone or in combination with other substances It was used against tapeworm infections and was tried in hookworm infections of dogs with good results a mixture of chloroform and castor oil for use in man did not prove to be effective though many worms were expelled [illegible]

[illegible] since the introduction of the active and comparatively less toxic carbon tetrachloride

Toxic symptoms

These resemble the symptoms seen after carbon tetrachloride Even 30 to 45 min produce unpleasant symptoms and as the dose is increased beyond 45 min the toxic effects become more marked Dogs, after two doses of 3 ccm each refuse food vomit are seized with mania like symptoms and die Extensive changes in the liver are not[illegible]
animals, the [illegible]
parenchyma [illegible]
and diaphrag [illegible]
but after abs [illegible]
occur Fatty [illegible]
case of carb [illegible]
irritation

A *mixture* of eucalyptus oil and chloroform was introduced under the name of Manson's mixture It contains eucalyptus 2 gm chloroform 2 gm, and castor oil 40 gm Most of the authorities who have tried this mixture agree that it is dangerous and not efficacious Exclusion of eucalyptus from the mixture does not lower its anthelmintic efficacy showing that the main action is due to chloroform

Iodoform has occasionally been used for removing ascaris in man in doses of 0.01 to 0.06 gm three times a day in combination with sodium carbonate Hall and Foster found this drug useless as an anthelmintic in dogs in much larger doses than those used in man.

Phenothiazine—This dye has been recommended by Manson Bahr (1940) for removal of ascaris in doses of 8 gm daily for 4 days in adults An after purge of sodium sulphate may be used if necessary

(3) The Essential Oil Group

(a) Oil of Chenopodium

SYNONYMS AMERICAN WORM SEED, MEXICAN TEA

Chenopodium has been used as a household remedy against intestinal parasites for a long time It was used by American Indians in the days of Columbus The oil was originally used many years ago against ascaris, but was not popular because of the toxic and sometimes fatal effects produced in many cases Schuffner and Verwoort (1913) tried it against hookworm in Sumatra in doses of 3 ccm in combination with castor oil and chloroform with excellent results From that time the drug came rapidly into use It came to the forefront during the First Great War when the supply of anthelmintic drugs such as santonin and thymol was curtailed On account of its toxicity it is not much used now

The active oil is obta ... m, or the *American wormseed* belo ... amily A number of other species ... ial in the Austrian Pharmacopœia ... *but only* two of them yield oil ha ... s and C *botrys* A variety of C

Chenopodium contain 40 to 80 per cent of *ascaridole* which is chemically allied to ... well as the toxic constituent The oil has no definite ... 0°C. in the air it explodes with violence Different ... characters the colour may vary from pale yellow ... different stocks also varies greatly and the samples met with in the market ... rated up to the extent of 50 per cent The whole oil as well as ascaridole are practically insoluble in water and are very slightly absorbed on this quality its anthelmintic action is chiefly dependent Ascaridole is altered by heat into a less volatile substance which has much weaker anthelmintic properties Distillation should therefore be carried out with great care

Besides the volatile substances chenopodium also contains certain terpenes—limonene cymene and terpinene Specimens of chenopodium oil met with in commerce vary a great deal in activity on account of variations in their ascaridole content The drug now on the market is properly standardised

Oil of chenopodium like other volatile oils is diffusible and irritant to the skin and mucous membrane It has germicidal properties It kills protozoa and was at one time recommended in ar ... produces salivation and refle ... of the intestines are ... ses produce severe irri ... bed from the stomach ... ows ... kilo

The oil has a well marked effect on the central nervous system There is a ... irst a

transitory stimulation followed by a marked depression of the respiratory cardio vascular and other centres in the medulla Later, the higher centres are affected, giving rise to stupor and coma The special senses, especially sight, may be affected Cases of blindness and deafness have been reported after use of chenopodium oil

Whether given by the mouth or intravenously the oil is partly excreted by the lungs and partly by the kidneys The elimination is slow and neither the oil nor the products of its decomposition can be readily detected Small doses have a diuretic effect by mildly irritating the kidneys, large doses may set up inflammation and albuminuria Subcutaneous injections of the oil in animals set up renal irritation.

In vitro experiments show that the action of the oil is probably due to penetration through the cuticle and into the cells of the parasites resulting first in stimulation and then paralysis of the musculature In such dilutions as 1 in 5,000 to 1 in 10,000 there is at first tonic contraction of the muscles of ascaris, followed by relaxation and paralysis so that the parasites cannot resist the intestinal peristalsis. Experiments on earthworms show that the toxic effect is much greater at 37°C than at 21°C

Anthelmintic effect

Oil of chenopodium has a marked action on all kinds of intestinal nematodes but little or no action on large tapeworms It is particularly effective against ascaris and is as good an ascaricide as santonin,
if a complete cure is not effected
them and they must be expelled b
podium is a particularly useful dr
tetrachloride, but is about equally effective against ankylostomes In doses of 30 min it can be depended upon to remove about 90 to 95 per cent of necators and about 80 to 85 per cent of ankylostomes

The oil is not so effective against trichuris because of the situation of these worms in the colon and cæcum Large numbers of threadworms are expelled but here also the

Dosage and method of administration

The maximum dose of the oil is 3 ccm given in three doses of 1 ccm each at intervals of an hour The last dose is followed one hour later by an ounce of saturated solution of magnesium sulphate This dosage cannot be adopted in general treatment because it frequently gives rise to severe toxæmia especially in ill nourished patients

The drug may be given in the morning in doses of 10 to 15 min at 7 8 and 9 a m Some authorities allow an interval of 2 to 3 hours between the doses and some prefer to give the anthelmintic and purgative together 10 to 20 drops being given with senna or mixed with castor oil. To conceal the taste it may be mixed with olive oil or almond oil

Pure ascaridole is now on the market and is used in doses of 1 0 ccm for an adult given in 2 or 3 divided doses an hour apart Pessoa (1923) gave 1.0 ccm in one dose in hard gelatine capsules on an empty stomach followed by a saline purgative half an hour later, a preliminary purgative is not necessary For children up to 5 years 1 to 2 drops of ascaridole in an emulsion of 10 to 20 ccm of castor oil is the best For children between 6 and 15 years, one drop for each year of age in gelatine capsules followed an hour later by a saline purgative is generally recommended

gela
obta
ly
are not only as good but better if no preliminary dietary measures are adopted and no pre purgative is given This makes the oil a useful drug for labour forces in the field It is preferable to give the oil three hours after a moderately light morning meal

be given at least 2 hours after administration of the oil as it has been shown that simultaneous administration of salts greatly reduces the anthelmintic efficacy of the drug

Chenopodium has been tried intramuscularly and is said to have an anthelmintic effect when given in this way The mixture prescribed for this purpose consists of chenopodium oil 60 ccm camphorated oil 60 ccm and resorcin 4 gm The usual dose is 4 ccm of the *mixture injected into the buttock.* Its vermicidal action against hookworm is small but is quite efficacious against trichuris. Intravenous injections of the oil in doses of 20 ccm have been given with the idea that after absorption into the blood the oil will reach the hookworms which have anchored themselves to the mucous membrane and which will then let go their hold Given in this way the oil may produce a mild collapse

deafness and ringing in the ears After excessive doses extreme dizziness a feeling of intoxication prostration headache, drowsiness and unconsciousness occur showing that there is severe toxæmia The face is flushed respiration slow pupillary reaction sluggish and convulsions may follow giving place to flaccid paralysis Albuminuria is present in severe cases and there may be hæmaturia. Autopsy shows severe inflammation of the ... in, there are fatty changes ... Children

tion the toxic symptoms may appear a day or so after administration ... s may be produced by smaller doses several days apart In man death has been reported from ingestion of half an ounce or even less Tolerance is decreased by starvation and debility and increased by fixed oils

As soon as inordinate sleepiness and depression or any other symptoms of intoxication appear the administration of *the drug if all the capsules have not been given should* be stopped and a brisk purgative given The stomach should be quickly washed out There is no antidote known and the treatment is therefore entirely symptomatic Respiratory and cardiac stimulants *should be given*

Chenopodium oil should be given with caution and in small doses when disorders of *the heart and kidneys are present It is forbidden in chronic nephritis* and organic disease of the heart and where hepatic and gastro intestinal disorders are present Prior to the administration of chenopodium against hookworm it is better to administer iron and arsenic and *liver extract especially when the patients are anæmic*

PREPARATIONS

Oleum chenopodii (U S P X) It is distilled with steam from the fresh above ground parts of the flowering and fruiting plant of *Chenopodium ambrosioides* Dose 10—30 min *(1 to 2 ccm) for children* as many minims as the number of years up to 10 years

Ascaridole (N O) Dose 1 0 ccm A synthetic ascaridole has been prepared which in doses of 4 drops for each year of age of children and 70 drops for an adult is an effective anthelmintic

(b) Other Essential Oils Used as Anthelmintics

A number of essential oils have been used in the treatment of intestinal worms but none of them have any specific action against any of *the parasites*

Eucalyptus oil

Oleum eucalypti The oil is distilled from the leaves of *E globulus, E dumosa* and a number of other species The chief constituents of the oil are pinene eucalyptol (cineol) and aldehydes of fatty acids It has been used as an anthelmintic in combination with chloroform but its action appears to be very mild Caius and Mhaskar (1920) gave it in

Cajuput oil

Oleum cajuputi Cajuput oil is a volatile oil distilled from the fresh leaves and twigs of *Melaleuca leucadendron* var *minor M viridiflora* It is a green coloured oil with an aromatic odour and a pungent taste The chief constituents are cajuputol which is the same as eucalyptol or cineol, terpineol, small amounts of pinene and traces of aldehydes The oil has therefore, the same active principles and same action as oil of eucalyptus

It has been used as an anthelmintic in the gold mines of Guiana in the treatment of mild hookworm infections Caius and Mhaskar (1920) tried the oil and found that even in 60 min doses (the maximum tolerated dose) hookworms were very feebly affected and ascaris and whipworms were not attacked at all The oil of cajuput cannot, therefore be recomended as an anthelmintic

Oil turpentine

Oleum terebinthinae Common turpentine is an oleoresin obtained from several varieties of pines chiefly from *Pinus palustris* There are several varieties of turpentine oil on the

poses Pure oil
ielmintic dose is
imes prescribed,
cinamon water

be administered

As an anthelmintic the oil of turpentine in doses of ½ to 1 ounce has been successfully used in man Some authorities have discouraged its use on the ground that it is likely to produce nephritis during excretion In large doses as used for expelling worms it acts as a purgative and is not absorbed in sufficient quantities to cause renal irritation Tapeworm infestations have been treated with one ounce doses in combination with castor oil

wit ... iookworm
wit ... therefore
aga ... enemata
con

Oil of Tansy

Oleum taneti (Tansy) This oil is distilled from the flowering tops and leaves of tansy *Tanacetum vulgare* belonging to N O Compositæ It is a yellowish brown liquid consisting of thujone borneol camphor and a number of resins It has been tried as an anthelmintic but is found to be wholly ineffective against hookworm ascaris and whipworms It is also a toxic drug and even in therapeutic doses produces vomiting and giddiness The leaves and tops of *Tanacetum vulgare* have been used in the form of an infusion or as an enema to expel ascaris and oxyuris

Oil of absinthi

Oleum absinthi The oil of absinth or vermouth or wormwood is obtained from the flowering tops and leaves of *Artemisia absinthium* belonging to N O Compositæ It is

were not encouraging

Oleum caryophylli The oil of cloves is a thick yellow oil distilled from the flower buds of *Caryophyllus aromaticus* The chief constituents of this oil are an unsaturated phenol called *eugenol* which forms 80 to 90 per cent of the oil acetyl derivative of eugenol (2 to 3 per cent), caryophyllene, etc

The oil has been tried against hookworms with little success Caius and Mhaskar (1922) by using an oil containing 92 per cent eugenol in the form of an emulsion obtained satisfactory results With 90 *min doses* administered in divided doses at half an hour intervals 64 3 per cent of hookworms were expelled, necators being much more vulnerable than ankylostomes Oxyuris are also expelled in large numbers ascaris and trichuris are not affected.

Pure eugenol and iso eugenol have also been tried and found to have well marked vermicidal action against hookworms *their action resembling thymol* Both are well tolerated in doses of 1 to 1½ drachms and with such dosage they produce a mild purgative effect thus obviating the necessity for an after purgative

Oleum betulae Betel oil is an essent[illegible]
known as 'pan' Leaves of this plant [illegible]
of *eugenol* [illegible]
30 to 90 [illegible]
20 per cen[illegible]
belief rega[illegible]
tion of [illegible] hookworms from the body by constant spitting and so preventing them from migrating from the trachea into the œsophagus

Oleum sassafras The oil of sassafras is an essential oil distilled *from the root of Sassafras* [illegible]
resembling tho[illegible]
expels 52.4 per [illegible]
chenopodium o[illegible]
been used in 60 [illegible]

Oleum anisi This is obtained from distillation of ripe fruit of *Pimpinella anisum* The oil is mainly composed of anethol but also contains small quantities of terpene Its action closely resembles that of thymol It is a fairly good vermicide the maximum dose of 60 min expelling about 50 per cent of hookworms

Pure anethol has also been used and is quite effective against hookworms expelling as many as 70 per cent of the parasites No toxic symptoms are met with either with the oil or with the active constituent anethol even in one drachm doses

Oleum cinnamomi The oil is derived from *C zeylanicum* and it contains large quantities of cinnamic aldehyde (50 per cent) and is a powerful germicide The oil has been tried but with disappointing results against ascaris trichuris or hookworms

Oleum rutae The oil is derived from the fresh leaves of common Rue, *Ruta graveolens* It was used as an anthelmintic in India and is still used in some parts the juice of the plant being given to children to expel intestinal parasites Its anthelmintic efficacy is however, slight.

Oleum copaiba It is quite useless as an anthelmintic even in doses of 30 to 60 min. against ankylostomes, necators, ascaris and trichuris

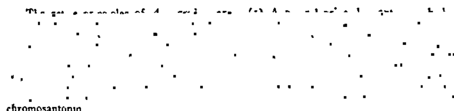
(4) Santonin

Santonin is a classical remedy for the treatment of ascaris and oxyuris infections It is obtained from *Artemisia maritima,* a plant whose flowering tops were used by the ancient Greek and Roman physicians as a remedy to expel intestinal parasites Santonin is one of the most expensive drugs Before the War practically the whole of santonin supply of the world came from Russian *Artemisia cina*

A number of allied species such as *A maritima* var *stechmanniana* and *A pauciflora* (*A anthelmintica*) also grow in Turkestan. Owing to political and economic disturbances in Russia some years ago there was great scarcity of santonin and *A cina* having good santonin content was successfully cultivated in Holland. *A maritima* or *A brevifolia* grows

abundantly in a state of nature in the dry inner valleys of the western Himalayas from Kumaon to Kashmir at an altitude of 4,000 to 12,000 feet above the sea level, and recently santonin has been obtained on a commercial scale from this source. Large quantities of artemisia with high santonin content are found to grow wild in the Kurram valley in the North-Western Frontier not far from the railway line.

Chemical composition and properties



chromosantonin

Pharmacological action

Externally santonin has very little action. Taken by the mouth it is tasteless at first but develops a bitter taste after a short time. Santonin unlike most other anthelmintics is not a gastro-intestinal irritant. It is quickly absorbed from the empty

rabbit. The animal usually dies of asphyxia from stoppage of respiration. Santonin is chiefly eliminated in the urine partly unchanged and partly in the form of oxysantonin which gives the urine and sometimes the fæces a deep yellow colour. This colouration

may go on for several days.

In vitro ascaris are not killed even by saturated solutions of santonin in olive oil or castor oil. The parasites, however, become irritated and try to escape from the proximity of the drug. The irritant effect of the drug causes the parasites to move about in their

on the parasites.

Santonin as an anthelmintic

Santonin is considered the most effective drug against ascaris, with the possible exception of oil of chenopodium and hexylresorcinol. It is useless in intestinal tæniasis. Santonin acts best when combined with 3 or 4 grains of calomel and followed by a saline purgative six hours later. Calomel stimulates the flow of bile which enhances the toxic action of santonin on the parasites. Santonin is best prescribed in the form of a powder either as coarse crystals or as trochisci. In the form of coarse crystals as ordinarily sold it is preferable to the finely divided powder, as the latter is liable to produce toxic symptoms. Alkalies dissolve it forming soluble alkaline santoninates which are usually absorbed rapidly, and therefore this combination should be avoided.

In determining the dosage for children a good rule is to give 1/6 grain for every year of age, for adults 1 to 5 grains according to the general constitution of the patient may be given *The preliminary* preparation of the patient and after purgative are most important considerations in santonin administration The following procedure has been used successfully at the Calcutta School of Tropical Medicine —

The patient is given *his last meal at 5 p m no food being allowed* after that *In severe infections it is advisable to keep the patient on light diet for* 24 hours previous to administration of the drug At 10 p m 3 grains (0 2 gm) of santonin combined with 3 grains (0 2 gm) of calomel are given At 6 a m the following morning ½ to 1 ounce saturated solution of magnesium sulphate *or sodium sulphate is given The stool should be examined for 72 hours after* treatment for the worms and should be re examined about 10 days later for ova, if negative the patient may be considered cured The drug is toxic and not very effective and is being replaced by hexylresorcinol

followed by vomiting may be produced cured in one series Santonin is a ion It is therefore recommended *no sensitiveness is shown the drug* may be repeated

Some authorities give santonin combined with an equal or larger doses of calomel every morning for 2 or 3 days in succession and repeat the process every 3 or 4 days as long as eggs are found This procedure is likely to lead to toxic effects Some observers consider it inadvisable to use an oily purgative such as castor oil with santonin as it is likely to increase absorption others consider that it inhibits absorption

ntonin red by m and gative adult oil of

The same workers (1938) working on the efficacy of oil of chenopodium and santonin opined that reduction in the *amount of santonin has* little effect compared with that which follows a reduction in the amount of oil chenopodium

Santonin is a toxic drug and should on no account be prescribed unless the diagnosis is made by thorough examination of the stools The practice of prescribing santonin on the mere assumption of parasitic infestation is to be deprecated

Subcutaneous intramuscular and intravenous injections of santonin sodium' have been successfully tried against ascaris

reatment of amœbic ter condition

to 10 grains (0 6 gm) daily Patients susceptible to the drug shou ed by giving ½ grain (0 03 gm) and it should not be continued for more than 10 days Santonin also relieves the lightning pains of *tabes dorsalis the initial* dose for this purpose being 1/120 to 1/60 grain (0 5 to 1 0 mgm) It has been used in the treatment of epilepsy in doses of 2 to 5 grains (0 12 to 0 3 gm) In small doses of 1/60 to 1/6 grain (1 to 10 mgm) it has been recommended in the *treatment of retinitis*, amblyopia and colour blindness on account *of its stimulant* action on the retinal nerves

Toxic effects

Symptoms of santonin poisoning vary from slight manifestations of anomalies of vision to convulsions coma and death In mild poisoning digestive and ocular disturbances alone are observed, but in severe cases disturbances of the central nervous system predominate Headache, vertigo, mental confusion, hallucinations, weakness, profound prostration, ... ten profuse ... The heart ... essure due ... nd urinary ... Tremors,

Treatment of poisoning

Treatment of poisoning consists in rapid and thorough emptying of the bowels by purgatives and an enema. A central emetic like apomorphine may be given Stimulants such as atropine caffeine, or camphor, may be administered and the patient kept warm If convulsions are present repeated doses of chloral hydrate or inhalations of chloroform or ether may be tried If respiration fails artificial respiration should be resorted to

Precautions and contra indications

It is advisable not to give santonin on an empty stomach as it is soluble in the gastric juice and may be absorbed It is preferable not to give it with an oily cathartic Fever is not a contra indication to the administration of this drug

Preparations

Santonica with a santonin content of 1 5 to 3 per cent is used in ½ to 1 drachm (2 to 4 gm) doses as an anthelmintic

A combination of santonin and bile called *santonin bile* has been prepared but it may produce toxic symptoms from rapid absorption.

Santoninum Dose 1 to 3 grains, U S P dose 1 grain (0 06 gm), in the French Codex 1½ grains as a single dose, the maximum dose given during 24 hours being 5 grains *Chromosantonin* (N O) or golden santonin is a modification of ordinary santonin formed by exposure to sunlight The dose is the same as ordinary santonin and it is stated to be useful in sprue and dysentery *Trochiscus santonini* contains 1 grain in each Dose 1 to 3 *Trochiscus santonini Co* contains ½ grain of santonin and calomel each Dose 1 to 2 grains

... with ginger, jalap sulphur ... nin half an ounce of castor ... scribed on an empty stomach

Sodii santoninas Dose 1/50 grain (1 mgm) cautiously increased to 1/20 or 1/10 grain (3 to 6 mgm) is used for systemic effects As an anthelmintic 1/4 to 1 grain for adults preferably in salol-coated pills

Calcii santoninas (N O) Dose 1 grain It is a white tasteless insoluble powder

Artemisine in doses of 1/600 grain (0.0001 gm) has been used as a gastric stimulant

(5) Thymol and Allied Compounds

A number of compounds belonging to the stearoptene group, including menthol, borneol, camphor, and thymol have been tried as anthelmintics but only the last named is effective It has been shown that so far as these compounds are concerned, (*a*) the hydrogenation of benzene decreases their anthelmintic action, but increases their toxicity to the host, (*b*) the total destruction of the benzenoid structure leads to the formation of toxic compounds with no anthelmintic properties, (*c*) esterification of the phenolic hydroxyl group leads to formation of non anthelmintic and non toxic compounds, *e g*, thymotal

(a) Thymol

Thymol was first tried in the treatment of hookworm infections by Bozzolo in 1879 Since then it has been extensively used with satisfactory results In recent years, however, oil of chenopodium, carbon tetrachloride and tetra chlorethylene have largely supplanted this drug, for they are more effective and less dangerous than thymol and can safely be used for mass treatment and labour forces

Thymol or thyme camphor is *contained in a number of essential oils from many plants*, the chief amongst which is *Thymus vulgaris*, an evergreen shrub belonging to the Labiatæ family In India thymol is manufactured on a commercial scale from *Cuminum cyminum* which contains large quantities of cumin o
can be *readily converted into thymol* Th
also contains not less than 40 to 50 per
growing in America contains 60 per cent
contains 60 to 67 per cent

The chemi ... roptene
It is a higher h ... soluble
in water (1 in ... contact
with menthol (

The action of thymol is similar to that of phenol it has about one fourth the antiseptic power of phenol and in concentration as low as 1 in 10000 kills free living protozoa such as paramœcia It is fatal to staphylococcus aureus in 0 5 per cent concentration to typhoid and anthrax bacilli in 0 8 per cent and pneumococcus in 1 per cent. Growth of putrefactive bacteria is prevented by 0 1 per cent solution and 1 0 per cent is required to kill them It inhibits the growth of moulds in 0 02 per cent solution

Externally thymol has no action on the unbroken skin but it can exert its caustic or irritant action on mucous membranes When taken internally in ordinary anthelmintic doses it produces a feeling of well being and comfort in the stomach, there is reflex stimulation of the peristaltic movements of the intestines The presence of fatty constituents in the intestines promotes absorption of *thymol* and *if this absorption is large it gives rise to* systemic effects and produce fatty degeneration of the liver It is therefore advisable to avoid fats alcohol glycerine etc when thymol is being administered

follow when large quantities are absorbed

Given by the mouth in doses of 15 to 30 grains (1 to 2 gm) most of the thymol is absorbed for none is found in the fæces About half of the drug ingested is excreted in the urine partly in combination with sulphuric and glycuronic acids partly unchanged and partly oxidised to a bivalent phe
in the urine after administratio

In vitro thymol has a powerful action on earthworms In 1 in 2,000 solutions the ... of irritation and their movements are markedly increased at first but ... killed

There is no unanimity of opinion about the effective dose of thymol Some au have recommended as much as 120 to 150 grains in divided doses of 25 to 30 grains while *others consider* such large doses are neither necessary nor justifiable They do not advise more than 60 grains of thymol in a day and recommend not to repeat *it in less than a* week In pregnant women the dose should not exceed 30 grains and in cases of extreme debility from old age heart disease chronic diarrhœa and dysentery the dose should be

small and divided The drug should at once be stopped if untoward symptoms appear Ashford and King recommend the following scale of dosage —

Dosage

Under 5 years 8 grains (0 5 gm), 5—10 years 15 grains (1 0 gm), 10—15 years 30 grains (2 0 gm), 15—20 years 45 grains (3.0 gm), 20—60 years 60 grains (4 0 gm), over 60 years 30—45 grains (2 to 3 gm)

Method of administration

It is customary to give the drug in two or three divided doses, of 15, 20 or 30 grains each at intervals of 1 to 2 hours followed by a strong saline purgative It is better not

Preparation of patient

The preparation of the patient is important when thymol is being given as an anthelmintic. The following procedure is recommended (Ashford)

The patient is given a light meal and one ounce of saturated solution of magnesium or sodium sulphate the night before At 8-30 a m the following morning 30 grains (20 ... dose is given ... is given No ... The patient

Effectiveness

Thymol is the classical drug for the treatment of hookworm infections, but more than one course of treatment is often required to produce a cure In one series 68 6 per cent were cured in 30 days and 94 4 per cent in three months (presumably 4 to 8 treatments) The drug is believed to be more effective against mature worms Fourteen to fifteen days ...

death occurred

Maplestone and Mukerji (1940) after a comparative study, conclude, that though the efficiency of thymol is undeniable, yet considering the cheapness safety of patient, simplicity of administration, and proved efficacy against hookworms, tetrachlorethylene is the drug of choice

Effect on other nematodes

... stinctly inferior to its effect on ... ulnerable to its action Tape ... is very doubtful Thymol has ... when they are present in the ... parasites have lodged in the

Other uses

Toxic effects.

In large doses thymol produces symptoms resembling carbolic acid poisoning There is usually acute pain over the epigastrium due to the caustic and irritant action of the drug on the mucous membrane of the stomach, nausea and vomiting follow and the patient be-

comes prostrated Giddiness, roaring sounds in the ears drowsiness etc., commonly occur there is often salivation and cyanosis and the patient may become unconscious Th temperature has a *tendency to fall below* normal and both the pulse and respiration are slowed, skin rashes may appear, the urine may become scanty, abortion may follow in pregnant women With very large doses collapse may be rapidly produced and death may occur in a few hours The intensity of symptoms depends on the amount absorbed and the presence of solvents like fats and alcohol strongly increases the tendency to produce intoxication A purgative given a few hours after the drug prevents intoxication by washing it out of the gut Sometimes the intoxication is delayed and sets in several days later when all the symptoms except weakness have disappeared

In poisoning the stomach should be rapidly washed out with warm water Demulcents may be given to prevent corrosion of the mucosa Cardiac and respiratory stimulants, *e g* 1/120 grain (0·005 gm) of atropine and 1/30 grain (0·002 gm) of strychnine should be given Hot coffee is useful in overcoming weakness Alcoholic stimulants and tinctures are contraindicated

Thymol should be given with caution when there is anæmia nephritis advanced cardiac disease, pregnancy and debility due to old age Patients suffering from chronic diarrhœa and dysentery also take it badly

Attempts have been made to lower the toxicity of alkyl phenols by converting them into non irritant esters such as carbonates carbamates etc Thymotal or thymol-carbonate is prepared by passing phosgene gas through a concentrated solution of thymol in an aqueous solution of caustic soda It was at one time considered to be a very effective remedy against ankylostomes but later it was found to be absolutely useless even in 40 grain doses Although these esters are broken up in the alimentary tract by hydrolysis forming the original hydroxyl compounds they do not attain sufficient concentration to be effective anthelmintics

Isothymol or *carvacrol* wa [illegible] he Great War
when the supply of thymol fr [illegible]
of thymol and its pharmacol [illegible]
respects The anthelmintic a [illegible]
with fairly satisfactory result [illegible]
its efficiency against hookworm [illegible]
doses with promising results [illegible]
to thymol It is also more irritant and somewhat more toxic than thymol

Thymol disinfectant (Martindale) It is a potent antiseptic, when employed as a general disinfectant 1 in 200 solution in water should be used

Liquor thymol is made of 1 part of thymol in 800 parts of warm water, used as an antiseptic gargle well diluted

Mistura oleobalsamica Dose is 1 to 4 drachms in water as a carminative stimulant
Pastilli thymol Contains 1/32 grain of thymol in each

Pigmentum thymol It consists of thymol 1 part ether 10 parts and spirit 5 parts or may also be prepared with petroleum oil useful in ringworm of the scalp

Thymoglycine It is a palatable preparation containing sodium benzoate menthol essential oils, glycerine and thymol water It is given in rhinitis pharyngitis quinsy, etc, or as a *spray for throat and nostrils* diluted 1 to 3 in water For colitis in children 5 to 10 min in paraffin or water are given

Glycothymoline It consists of potassium carbonate sodium benzoate, sodium borate sodium salicylate thymol menthol glycerine and alcohol coloured with cochineal It is frequently prescribed as an intestinal antiseptic in doses of ½ to 1 drachm and also as a gargle

Unguentum thymol Prepared in strength of 20 grains (1·3 gm) in an ounce of soft paraffin useful in eczema A compound ointment has boric acid and zinc oleate in addition

Thymol carbonate (Thymotal) It is a colourless and tasteless crystalline powder employed in ankylostomiasis in doses of *5 to 15 grains (0·3 to 1·0 gm)*

Thymoform is obtainable in the form of lozenges containing thymol and formic aldehyde in a cane sugar basis

(b) Beta-Naphthol

Beta naphthol has been used as an anthelmintic for quite a long time As early as 1904, Bentley used the drug against hookworm in Assam and later in 1908, Burkitt and Drummond tried it with excellent results The chief merits claimed on its behalf are that it is not unpleasant to take, it is more satisfactory for routine use and is one tenth the price of thymol Caius and Mhaskar reported very favourably on the drug and recommended it as the safest and most efficacious anthelmintic for hookworms, but subsequent work has failed to substantiate their claims With the advent of carbon tetrachloride and oil of chenopodium beta naphthol is gradually receding from the field though it is still used in some places.

Source and composition

Naphthol is derived from the hydrocarbon naphthalene by the substitution of a hydroxyl for one of the hydrogen atoms There are two naphthols—the alpha and the beta- naphthols —the former is very toxic and is not used in medicine

lamellæ It luble in cold and does not

Pharmacologic action

Externally beta naphthol is irritant to the unbroken skin and may be absorbed there

doses produce an irritant action on the gut and produce nausea and vomiting

The heart is reflexly accelerated at first, but later it becomes slower which is due to direct action on the cardiac muscle In large doses it has a toxic effect on the red blood corpuscles especially in patients with active or latent malaria The corpuscles may be destroyed in sufficient quantities to produce hæmoglobinuria, jaundice and severe anæmia Large doses depress the respiration probably from depression of the respiratory centre Therapeutic doses have no effect on the central nervous system, but after absorption of large amounts, it produces giddiness and convulsions followed by paralysis and coma Changes in the retina and opacity in the lens have been produced in some cases after its use

Beta naphthol is rapidly excreted in the urine and during its excretion it may produce inflammation of the kidneys, even when the doses taken are not large It is excreted in combination with glycuronic and sulphuric acids and imparts to the urine a dark brown or mahogany red colour Although salivation is produced it is not excreted in the saliva

Dosage.

There is great diversity of opinion about the toxicity and efficacy of beta naphthol as

the chances of production of untoward effects

Efficiency

Beta naphthol has been found by nearly all workers with the exception of Caius and Mhaskar to be less efficient than thymol and certainly less so than oil of chenopodium or carbon tetrachloride Usually at least four or five treatments are necessary before a cure is effected Its action on ascaris and trichuris is no more promising than its action in hookworms Smillie in Brazil removed only 52 of 124 ascaris (41 per cent) as compared with 91 per cent of 454 cases removed by chenopodium Tæniæ are also very little affected by it

Toxic effects

vulsions and coma with stertorous breathing have been seen even in non fatal cases

and fever Micturition is painful the urine becomes very dark, scanty and shows the presence of bile, albumen and casts, suppression of urine may supervene producing uræmia The spleen the liver and the kidneys are enlarged and hyperæmic, and the gall bladder is distended Death may occur from convulsions or gradual failure of respiration the heart goes on beating after the respiration has stopped All these symptoms are more readily produced in malarial patients The Porto Rican Anæmia Commission tried the drug extensively and found that 83.3 per cent of their cases who took it suffered from albuminuria *Caius and Mhaskar (1921)* noted that all their cases of albuminuria and hæmoglobinuria occurred with doses over 60 grains administered for several days With small doses no such symptoms were produced

The urine of patients should be always examined before administering the drug and if the kidneys are damaged *it should be given with caution Large doses should not be* given to those who are suffering from or have suffered from malaria.

ns (1 to 2 gm) is usually given or *beta naphthol* form of cachets *Benzonaphthol* as diuretic and intestinal antiseptic Dose 15 grains (1 0 gm) *Beta naphthol petroxalin* (N F) 100 gm of beta naphthol dissolved in 90 gm of liquid petroxalin used as a parasiticide application *Naphthalenus* (N O) has been tried against hookworm but has no anthelmintic action Dose the same as beta naphthol *Naphthalene tetrachloride* was tried in 8 grain (0 5 gm) cachets every 4 hours in colitis

(6) Resorcinol Derivatives

A number of synthetic compounds have been prepared and some, the isohexyl derivatives of either resorcinol or phlorogluein, are promising

(a) Hexylresorcinol

Hexylresorcinol is 1 3 dihydroxy -4- hexylbenzol It is a white waxy crystalline substance and is quite stable It is sparingly soluble in water (1 in 1,700) but it readily dissolves in alcohol, ether, chloroform and vegetable oils Hexylresorcinol is considered to have highly germicidal properties, the phenol co efficient varying between 46 and 52 It has been used as a mouth wash gargle, nose and throat spray in concentration of 1 in 4 000 It has been administered in gelatine capsules in doses of 0 45 to 0 6 gm three times a day, as an urinary antiseptic The drug has been continued for as long as ten weeks without showing any deleterious effects For children, a 2½ per cent solution of the drug in olive oil under the name of Caprokol (N N R) has been prescribed two or three times a day It has been highly spoken of in cystitis and pyelitis and appears to be well tolerated

It is said to be a safe and effective anthelmintic in nematode infestations, both round worms and hook worms It is given in doses of 15 grs in adults in hard gelatine capsules to avoid irritation of the mouth According to some, even given in this way, there is danger of necrosis of the gastric mucosa when the gelatine dissolves As the drug combines with the food, dieting is essential

Crystalline hexylresorcinol has irritant properties and is liable to produce a burning sensation in the mouth The irritating property of the drug can be overcome by dissolving it in olive oil but this reduces its vermicidal power A solution of 0 1 per cent of hexyl resorcinol *in vitro* killed pig ascaris in 2 minutes while it took more than 20 minutes to

be effective in 3 per cent olive oil solution Repeated administration to dogs is known to have produced petechial hæmorrhages in the buccal and gastric mucous membranes The drug is however precipitated by proteins and probably on this account it does not penetrate deeply into the tissues When given with alcohol absorption is facilitated Experiments on dogs show that about 27 per cent of hexylresorcinol taken by the mouth is excreted in the urine and 67 per cent is eliminated in the fæces

Anthelmintic properties

The anthelmintic property of the drug has been noticed only recently Lamson and [illegible] the local irritant effect, the maximum dose being 1 0 gm for adults magnesium sulphate being given two hours after They succeeded in curing 7 out of 10 cases the egg reduction amounted to 96.4 per cent in a total of 5 cases all of whom were cured The reduction was cent per cent if the purgative was deferred for 24 hours Food, shortly before or after the treatment greatly reduces its efficacy Lamson and his co-workers (1932) in evaluating the comparative results of hexyl and heptylresorcinol considered the former to be a better anthelmintic Lamson Brown and Ward (1932) consider a single dose of hexylresorcinol to be capable of removing more than 90—95 per cent of ascaris, 80—85 per cent of hookworms and 40—45 per cent of trichuris Maplestone and Mukerji (1932) using the drug in hard gelatin capsules under strict fasting conditions obtained a cure rate of 66 6 per cent and an egg reduction of 94 per cent in 21 cases In hookworm infestation in 26 cases the corresponding figures were 77 and 71.4 In ten cases of tæniasis no head was recovered after giving the drug but five reported no recurrence 3 months later

Method of administration

Dosage

Post purge

Before administering the drug proper dietary preparation is necessary In the evening previous to the commencement of the treatment, only milk and bread should be given. Early next morning hexylresorcinol is given in hard gelatin capsule in doses of 1 0 gm with about 2 ounces of water to help in swallowing the drug No food is allowed for 4 to 5 hours and alcohol is forbidden Reaction between the drug and gelatin can be avoided if the capsules are filled immediately before they are administered Sugar coated pills each containing 0 2 gm are available and they are unaffected by climatic conditions They are quite convenient to use except that in children they may cause a superficial burn in the mouth if they are chewed on account of the protein precipitating property of the drug when it comes in contact with the mucous membrane In the majority of cases, hexylresorcinol exerts a cathartic action and the patient has watery stools after it A dose of magnesium sulphate should however be given next morning *i e*, 24 hours after the dose The toxic symptoms observed are negligible Some of the patients may complain of pain in the epigastrium but this is very rare even with doses as high as 2 gm for a single administration Repetition of the dose even at short intervals in maximum quantity does not produce any toxic symptoms Hexylresorcinol so far as is known has proved of value in ascariasis in ankylostomiasis and other helminthic infection its superior efficacy over other drugs has yet to be worked out Probably in hookworm infection in anæmic and debilitated subjects it may be a safer drug than the other remedies in use

Hexylresorcinol is the nearest approach to an ideal anthelmintic drug and is therefore the drug of choice in ascaris and other infections Its toxic effects are few and are mild, there are no cumulative toxic effects contraindications are few The drug can be administered when the patient is up and about Its efficiency against ascaris equals any of the known drugs and it is also effective against hookworm though not equal to tetrachlorethylene It is administered in maximum doses of 1 0 gm (15 grains) Two doses administered at intervals of two weeks in ascaris infection cure the majority of cases A single dose

expells a large number of hookworms When these two infections are present together it is an ideal drug

The dose in children is 0 1 *gm for every year* of age up to 10 years

In tapeworm infections it is also effective and it has been successfully used against *Fasciolopsis buski* and whip worms In oxyuric infections it is given by the mouth combined with high enemata of hexylresorcinol solution

The pills should not be chewed as they set up irritation of mouth, they should be put far back on the tongue and swallowed The drug should be given on empty stomach and food should be withheld for four hours after administration It is also advisable to give a saline purgative the evening before, but an after purgative is not necessary except 24 hours after the drug to expell dead worms The following routine of treatment is prescribed for hookworms and round worms

(1) The day before, magnesium sulphate is given in the afternoon (castor oil is contraindicated) Patient is kept on liquid diet the whole day

(2) On the day of administration no food or drink is given till the drug is given Total dose is given at one time No food or drink for four hours after but fruit juice may be allowed with plenty of sugar Light food to be taken that day

(3) For tapeworms three full doses on alternate days followed by a saline purgative are best In enterobius infections, the drug is combined with soap enema or high enema with 1—2 000 solution of the drug which is retained for 20 minutes if possible After enema wash and dry anal region to prevent irritation

(b) Heptylresorcinol

On account of the results of hexylresorcinol in the treatment of helminthic infestations other alkyl resorcinols have also been used Heptylresorcinol is one of them Locally it produces a smarting burning effect on the tongue and is irritant to the buccal and gastric mucous membrane About 90 per cent of heptylresorcinol is excreted in the fæces Lamson and his co-workers (1932) in a comparative study of the effect of the two resorcinols in helminthic infections found that hexylresorcinol seemed more effective against hookworm ascaris and trichuris than heptylresorcinol The average egg reduction in hookworm disease with 1 0 gm doses of heptylresorcinol was 55 2 per cent in ascaris 73 5 per cent and in trichuris 35 8 per cent

Hookworm inf
oil In a series of
with olive oil soluti
in gelatin capsules
proved refractory

generally given in hard gelatin capsules in doses of 1 0 to 1 5 gm
ty stomach and food is withheld for 4 to 5 hours
lowers its efficacy A purgative should be prescribed
lso been prescribed in gelatin capsules coated with
lrug in the stomach so that it may reach the parasites
ration The results of treatment are more favourable
isis or tapeworm infestations

Hexylresorcinolis (tablets 0 2 gm) *Liquor Hexylresorcinolis* (1 in 1 000)

(7) TRIPHENYL METHANE (ROSANILINE) DERIVATIVES

The compounds most interesting from medical point of view are those which result from the introduction of amino groups forming pararosaniline Three closely related compounds thus formed are gentian violet, crystal violet and methyl violet Gentian violet is probably a mixture of methyl violet and crystal violet

Gentian violet was introduced as an antiseptic for infected wounds, mucous membranes and serous surfaces It is particularly useful in empyema and arthritis in which *staphylococci*, *Ps aeroginosa* and *Cl diphtheria* are causative agents *It also has an anthelmintic action*

Gentian Violet in Helminthiasis

This drug has now been tried extensively but is still in experimental stage It has been found to be specially effective in the treatment of enterobius infections As compared with hexylresorcinol enemas it is simpler to administer and more effective It is also effective against *strongyloides* and has been successfully tried against *Clonorchis sinensis*

T[illegible]
in fo[illegible]
effect [illegible]
occured in some patients [illegible] effects, however, soon pass off after the drug is stopped and the treatment can be resumed after a few days The drug should not be given when ascaris infection coexists with enterobius infection It is contraindicated in disease of the heart kidney and the gastrointestinal tract Alcohol is forbidden during the course of treatment with this drug

Mode of Administration

[illegible] 0 016 gm) and ½ gr [illegible] the proceedure is to [illegible]ls for fourteen days [illegible]irse of fourteen days is repeated For adults weighing more than hundred pounds, 1 gr (0 06 gm) tablets are given three times a day one hour before meals for seven days, rest for seven day and then the course is repeated altogether fifty grains being taken For strongyloides and clonorchis infection the drug is taken in doses of one grain three times a day for fifteen days In refractory cases tablets with one and one-half hour coating are used Faust (1939) suggested intravenous injections of 0 5 or 1 0 per cent solution in distilled water in refractory cases, and in bronchial and extra enteric strongyloides infections Injections were given in doses of 20 to 25 ccm every third day Violet colouration of the skin and fever may occur but these pass off Injections must be given slowly No untoward effects have been observed so far

Sostol—This is a yellow crystalline powder and is the hydrochloride of an acridine compound It is soluble and is said to be specially effective against diphyllobothrium and hymenolepis infections The patient is prepared in the [illegible]r) are given first thing in the [illegible] dose of castor oil or magne- [illegible] receive 1 to ½ pellets, and

(8) MISCELLANEOUS ANTHELMINTICS

Intestinal antiseptics Some of the compounds which show well marked disinfectant properties in the gastro intestinal tract
excellent a
septics beh
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that these drugs with the possible exception of some of the propenyl derivatives of phenol and salicylic acid esters are useless as far as their anthelmintic activity is concerned Some of these are positively dangerous to the host instead of being in any way inimical to the parasites

Potassium permanganate in maximum doses bismuth carbonate, kaolin naphthalene phenocoll, methylene blue, guaiacol carbonate creosote izal salicylic acid, salol acetyl salicylic acid (aspirin) salicylic ester of beta naphthol (betol) the crude phenols etc., have all been tried and found to be useless

Methyl salicylate, a volatile ester of salicylic acid has however, well marked vermicidal
effective
ylate is
It has

A number of propenyl phenols occur in nature, *e g*, anethol eugenol, etc These are fairly good anthelmintics and do not possess the toxic properties on the host, of the crude phenols

Purgatives These drugs have got very little vermicidal action but they irritate the

daily on each of these days After four days of treatment the enema is continued for two days more

Heavy metals A number of other drugs have been used for their anthelmintic effects in man and animals Copper sulphate has chiefly been used in veterinary practice, especially in infection with *Haemonchus contortus,* the stomach worm of sheep The arsenical compounds such as stovarsol have been given but their vermifugal effect is doubtful Injections of organic arsenicals and tartar emetic have been found to have some effect *on clonorchis infections in man Salvarsan and sulpharsenol injections have been given* in oxyuris and guineaworm infections with success in some cases Mercurochrome has been given intravenously against *Schistosoma japonicum* in man in 1 0 per cent solution with some degree of success

Embelia ribes and *E robusta* family Myrsinaceæ had the reputation of vermicidal action but they have been shown to be quite ineffective against hookworms round worms and whipworms The chief constituent of the fruit is embelic acid which occurs in golden yellow crystals resin and tannin Anthelmintic dose 1 to 4 drachms (4 to 10 gm) of the powdered drug

Azadirach The bark and root of *Melia azadirachta* has been used as an anthelmintic against roundworms The active constituent of the drug is margosic acid and a resin *In India and* in the southern United States the fresh bark of the root is employed to expel ascaris The powdered bark is given in doses of 20 grains (1 3 gm), or the decoction (made by boiling 2 ounces of the bark in a pint of water until reduced to half) is given in one tablespoonful doses hourly or every second or third hour, a purgative is *given after* the second or third dose The oil has no anthelmintic properties In excessive quantities the drug produces dizziness, purging and collapse

Corsican moss (helminthochortan) is a mixture of various marine algæ and is used in France and Italy to expel ascaris *It is* best given as a sweetened decoction with *milk in a single* dose before breakfast Dose for a child under two years is 15 to 45 grains (1 to 3 gm), of 10 years 3 to 4 drachms (12 to 15 gm) It is sometimes combined with santonin or santonica

Mucuna

Mucuna or Cowhage is the fruit of *Mucuna pruriens* a climbing plant of tropical America. The pod is covered with stiff hairs which produce intense itching Cowhage acts mechanically the hair piercing the parasites The pod is dipped in molasses and the hairs are removed by scraping Dose is one teaspoonful for a child and one table spoonful for an adult. The drug has been used both against roundworms and tapeworms but it is too disagreeable to take and too uncertain in its action

Butea frondosa

Butea frondosa has been used as an anthelmintic against roundworms but opinions differ regarding its efficacy The seeds have been analysed and they contain 16 per cent of a fixed oil called *moodooga oil* small quantities of resin and large quantities of a watersoluble albuminoid There are no active principles of the nature of alkaloids neutral principles or glucosides The powdered seeds have been used as an anthelmintic in doses of 30 to 60 grains (2 0 to 4 0 gm) but they are unpleasant to take and often produce pain in the stomach vomiting and giddiness The oil and the resin were separately tested against hookworm and ascaris The alcoholic extract the oil and resin had no effect, but freshly powdered seeds produced good results in ascaris infection. Old worm eaten seeds met with on the market are inactive.

Ficus laurifolia

Ficus laurifolia has been recommended as an anthelmintic against whipworm in man in doses of 15 to 30 gm. The latex of this plant has definite anthelmintic properties and is worthy of trial The active principle is unknown though it probably resides in the solid portion of the latex In its natural state the latex forms a perfect emulsion of rubber and resinous substances it contains an albumin and substance of fixed composition yielding ammonia, which is probably responsible for its anthelmintic activity The latex unfortunately readily ferments and will only keep for 4 to 5 days though in an ice box it has been kept for several months The drug is very effective against whipworms (*Trichuris trichiura*) It may produce toxic symptoms colic nausea vomiting muscular cramps delirium syncope urticaria rectal and vesical spasms and partial suppression of urine

Quassia

Quassia is the wood of the trunk and branches of *Picraena* or *picrasma excelsa* *Picrasma quassioides* Benn is a common shrub growing in the sub-tropical Himalayas The active principles of quassia are substances called picrasmin and quassin

[illegible] It has been used as a [illegible] Mhaskar by giving 5 [illegible] ely powdered root to [illegible] has however been fo [illegible] decoction is given in the form of an enema, but quassia suppositories containing ¼ grain (0 016 gm) of the extract with a gelatin basis may also be prescribed Two grains of the extract of quassia in the form of a pill taken three times daily along with some purgative are also given to clear out threadworms

Spigelia marilandica

Spigelia marilandica or pinkroot is a plant belonging to the family Loganiaceæ which is widely spread all over the southern parts of the United States It was formerly considered as a powerful anthelmintic especially against ascaris

The constituents of the root are *Spigeline* which is a volatile alkaloid resembling nicotine and conine a bitter principle soluble in water a volatile oil and resin

Very little is known about the action of this drug The alkaloid is a gastro intestinal irritant and in poisonous doses it produces convulsions It is absorbed slowly from the gut and if combined with a purgative it does not produce any toxic effects Sollmann (1918) tested its activity on earthworms but his results were not promising Pinkroot is chiefly used as a vermifuge against roundworms and is said to be quite effective against them Careful experiments on animals have shown that it has no marked anthelmintic action against any of the parasites

Chrysanthemum cinerariae

Chrysanthemum cinerariae The active principle is said to be a good parasiticide it is non-toxic and non-irritant It is said to be useful in ascaris trichuris threadworm and tapeworm infections

Rhamnus cathartica

Rhamnus cathartica A syrup made from the berries with jalap is said to be useful in oxyuriasis.

Allium sativum The allyl compounds contained, produce complete paralysis of ascaris *in vitro* but their anthelmintic effects in man are doubtful

Geraniol in doses 0.3 ccm per kilo body weight has been tried in dog but has no effect. Various species of *Cambretum* occurring in Brazil extracts of *C quadrangularis* essential oils of *Tagetes minutus* and *Kyllinga odorata* were quite ineffective.

Acalypha indica Petroselinum sativum and *Quisqualis indica* have no anthelmintic properties

Rotylon It is an aromatic combination insoluble in water but soluble in alkalies, manufactured by Bayer Meister Lucius Ltd The drug is set up in capsules each containing 0.4 gm When taken in liquid form it produces a burning sensation in the tongue which is followed by one of prolonged anæsthesia The anthelmintic properties of this drug are under investigation

Vernonia anthelmintica Powdered seeds in doses of 30 to 60 grains have a weak vermifugal action against ascaris and a more powerful action against oxyuris The bitter substance isolated in doses of 3 to 10 grains has a weak vermifugal action against ascaris and a decided action against oxyuris When combined with calomel and followed by magnesium sulphate the vermifugal action is considerably enhanced The drug has no action whatsoever against the hookworm and tapeworms The anthelmintic properties of the drug against ascaris and even against oxyuris are weaker and in no way comparable *with some of the other compounds now in the British Pharmacopœia*

Phenothiazine (Thio diphenyl amin) has been recommended by Manson Bahr (1940) as an effective anthelmitic in ascaris and enterobius infections This thiazine dye is fine smooth pale yellow [illegible] in water Repeated small doses are consid[illegible] ones The dye is mostly excreted in urin[illegible] after its administration, it has been shown [illegible] dye is shown to be very suitable for children The dosage advised by him is 8 gms daily for at least 5 days for adults, 2 gm daily for 7 days for children under 8, and half this dose for children under 4

Others recommend doses of from 15 to 30 gr daily for a period of about 10 days It is said to be effective, but it is not certain that it is safe Its action appears to be cumulative, and it is capable of producing severe anaemia presumably by a toxic action on the bone marrow

The advantages claimed are that no dietetic restrictions are required and it does not seem necessary to use after purges

Diphenan is best known under the proprietary name of Butolan and is the carbamic acid ester of p hydroxydiphenyl methane It is probably the most effective anthelmintic for oral administration for thread worms It does not produce serious toxic effects The dose 0.5 gm three times a day for adults and about half this for a school child It is continued for a period of about two weeks and is very often successful

Organic arsenicals in helminthic infestations Some of the organic compounds of arsenic have been tried against intestinal parasites as well as in somatic infections Given by the mouth stovarsol is said to have a vermicidal action A 10 per cent solution of stovarsol has no effect on ascaris *in vitro* but when mixed with intestinal juices it becomes active. Injections of salvarsan have been used against clonorchis Intravenously, organic arsenicals have been tried against oxyuris as well as guinea worm infections, against intestinal and blood flukes they have been tried without success Neosalvarsan has been tried in hydatid disease in man without success Experiments on rabbits show that hydatid material given with salvarsan does not prevent cyst formation

Aniline dyes in helminthic infestations The use of aniline dyes as anthelmintics is yet in its infancy Methylene blue has been tried against

clonorchis in Japan with some degree of success *In vitro* experiments show that living flukes are susceptible to methyl violet, crystal violet and nile blue sulphate Methyl violet given intravenously to dogs stains the liver intensely and is excreted in the bile, but concentrations fatal to the worms are very toxic to the host; nile blue is even more toxic Mercurochrome 220 (hydroxymercuric dibromofluorescein) and gentian violet have also been tried in clonorchiasis The certified gentian violet (either penta methyl or hexamethyl pararosaniline or els [illegible] nitely toxic to the worms, and after [illegible] the mouth produces a definite decre[illegible] as 16 mgm per kilo are less effecti[illegible] iptoms of intoxication characterised by vomiting and loss of weight are produced, 35 mgm per kilo produce no toxic effects, but in heavy infections where there is much damage of the liver, 15 to 17 mgm per kilo is a suitable dose. In man the results are not so good Twenty ccm of a 1 per cent solution of gentian violet given intravenously, followed 3 days later by 30 ccm caused the disappearance of ova in one case

Among other dyes, malachite green, brilliant green crystal violet, fuchsine, congo red trypan red, trypan blue and thionin blue have been tried Both acid and alkaline dyes showed some toxicity on the cysticercus and on the larvæ, but no experiments have been carried out *in vivo*

Hetrazan—This is a synthetic piperazine derivative (1 diethylcarbamyl -4-methyl piperazine hydrochloride) Administered orally it produces marked and immediate (within 48 hours) reduction in microfilarial counts in the peripheral blood of cotton rats and dogs, infested with filarid worms The continued administration of the compound to cotton rats at doses of 10 to 25 mg per kg [illegible]

low (mice—LD_{50}—285 mg per kg given intraperitoneally, and 660 mg per kg given orally, rat—LD_{50}—465 mg per kg given intraperitoneally and 1380 mg per kg given orally)

It has been used in human filariasis (*Wuchereria bancrofti* infection) in doses of 2 mg per kilo body weight three times a day being orally given after food for a period of three weeks But in chronic cases this period may have to be extended Smaller doses are not advisable since it has been shown that recurrences after small doses are more frequent which is an indication that all the filariae have not been killed An average man weighing between 150 and 160 lbs would require 140 mg of hetrazan three times daily, *i e* 3 tablets (50 mg each) after each meal The microfilariae are greatly reduced in number by the second day of treatment Apart from action on the embryos evidence of [illegible]

exacerbation of usual filarial symptoms or sometimes other manifestations, which we consider of allergic origin and which must be produced by an increased amount of released filarial protein when the worm dies

Druing treatment anorexia, slight nausea, malaise, weakness, fever, shortness of breath, etc are sometimes seen but these usually pass off very soon In some cases nodular swelling, testicular pains with temperature, etc occur which are believed to be due to the death of the adult worms Hewitt has reported evidence of toxicity in man at dosage of 8 to 10 mg per kg given after a meal, in volunteers not infested with filariae, and with a single oral dose of hetrazan ranging from 6 8 to 10 9 mg per kg after a noon meal the following major symptoms develop malaise, nausea, drowsiness, lethargy, *vasoconstriction, apprehension increased* salivation and perspiration

This drug has also been used in *Onchocerca volvulus* infection in the same dose as in *W bancrofti* infection and is found to be *very highly* effective. Extensive testing of hetrazan in Mexico and Guatemala, where about 1/3rd of the population are infested with Onchocerca, has shown that this drug has a highly specific and rapid effect upon onchocerciasis. Side reactions following its use *for the treatment of this infestation have been fairly frequently reported* but are of short duration, and they are not commonly a signal for discontinuance of treatment The most convenient dosage is 2 mg per kilo body weight three times daily for 21 days Precautions must be taken in administering this drug *to patients suffering from onchocerciasis, since severe reactions after* a single dose may occur, dependent apparently upon the intensity of infestation Facial œdema, pruritis, and itching of the eyes are often encountered

Treatment of chronic and advanced cases No definite claims are made as yet for the usefulness of hetrazan in advanced clinical and elephantoid cases of bancroftian filariasis Preliminary reports from British Guiana, indicate that subjective symptoms may be relieved, and that enlarged glands may be reduced *in size after treatment* Treatment for a minimum of at least 4 weeks is advised in advanced clinical cases

Effect of hetrazan against other parasitic round worms of man and domestic animals It is effective however against several species of round worms other than filarids in both humans and domestic animals, thus in *ancylostoma braziliense* in man it is apparently effective in 2 mg per kg doses thrice daily for four weeks and in—*Ascaris lumbricoides* in man good effect is found at 2 mg per kg doses thrice daily for one day In *Dirofilaria immitis* in dog good effect is observed against microfilaria and partial effect against adults at 25 mg per kg doses thrice daily for four weeks In *Loa loa* in man it is effective in 2 mg per kg doses thrice daily for 4 weeks *In Acanthocheilonema perstans* in man [illegible]

The advantages of this drug for clinical use are (*a*) toxicity is low (*b*) specificity of the compound is very high for *Wuchereria bancrofti* and *Onchocerca volvulus,* (*c*) ease of administration is provided in that it may be given orally [illegible] where it is to be used under [illegible] 0 5 to [illegible]

PRESENT POSITION OF ANTHELMINTIC DRUG THERAPY

Although a large number of anthelmintic drugs have been introduced during recent years only a small group of them are really effective without undue toxicity

I *Anthelmintic drugs acting on tissue parasites*

There are only a few drugs which have any marked degree of effectiveness on tissue helminths Antimony compounds have a powerful action in schistosomiasis Antimony tartrates of sodium and potassium are used the former is considered to be less toxic These drugs are used in the same way as in Kala azar in 2 per cent solutions The average dose for an adult is 2 ccm given intravenously gradually increased to 5 ccm 15 to 20 injections or more may be required to eradicate the disease A preparation named fouadin or stibophen (sodium salt of antimony bispyrocatechol sodium disulphonate) is less toxic and has the advantage that it can be given intramuscularly The first dose is 1 5 ccm the second 3 5 ccm and subsequently 5 ccm A total of 40 to 60 ccm are required Following upon healing in a week or two the course may have to be repeated and thereafter the drug is given once a week and then every fortnight to prevent relapses The drug is sold in ampoules containing 3 5 and 5 ccm (each 1 ccm containing 0 064 gm of fouadin) Emetine has also been used by intramuscular and intravenous routes for eradication of some of these infections but this drug is too toxic gentian violet medicinal has been used by the mouth and intravenously but is still in experimental stage

II *Intestinal parasites* —

For the treatment of intestinal worms however there are some quite effective remedies General instructions for use of these drugs are —(1) A definite diagnosis should always be made first based on demonstration of ova larvae or segments of the parasite before treatment with these drugs is started (2) All anthelmintic drugs are toxic and should be used with the greatest of care especially when pregnancy debility disease of the lung kidney liver infectious fever are coexisting conditions (3) Alcohol and fats favour absorption of some of these drugs and toxic effects are increased These should therefore be forbidden (4) A saline purgative especially magnesium sulphate is best used with these drugs Purgatives however are contraindicated in inflammatory conditions of the gut (appendicitis etc) If constipation is present bowels should be evacuated with an enema Magnesium sulphate should be given on the preceding night and again in the morning 2 or 3 hours after the anthelmintic drug has been administered If however vomiting occurs and toxic symptoms appear it should be given at once Many of these drugs act best when given on an empty stomach Food should not be given till the bowels evacuate Exceptions to this rule are hexylresorcinol in which food is witheld only for four hours after the administration of the drug and gentian violet which needs no purgative (5) The drug selected should be one which is most effective in eradicating the particular parasite has least toxicity and causes least inconvenience to the patient

Instruction for use

Of the older drugs oleoresin aspidium even now is one of the best available for removal of tapeworms The drug is especially dangerous in children with dwarf tapeworm infection and in such cases hexylresorcinol is preferred. Male fern should be given after proper preparation for two days before administration, the oleoresin is given in doses of 20 minims (1.25 ccm) in 3 doses in

Aspidium

capsules at half hours interval in the morning on empty stomach followed two hours after by a saline purgative Food is permitted after the bowels have been thoroughly evacuated (after one or two copious motions) Oleoresin can also be given in form of an emulsion oleoresin 1½ dram (or 6 ccm) powdered gum acacia 2 drams (8 0 gm) and water two ounces (60 ccm) This is divided into two portions and given at interval of half an hour In children one dram or 4 ccm of the emulsion is given for every ten pounds of body weight

Recently carbon tetrachlorid in doses of 3 cc shaken with one ounce of saturated solution of magnesium sulphate has been used in tapeworm infection and found to be effective Owing to the unstable nature of oleoresin aspidium and toxicity carbon tetrachloride is preferable

Tetrachlorethylene is the best drug in hookworm infection when ascaris infection does not exist at the same time The drug is given in gelatine capsules each containing 8 min (0 5 ccm) and to children it may be given on sugar In mass treatment it is best given in a saturated solution of magnesium sulphate Dose for adult is 45 min (3 ccm) for 10 to 15 years 30 min (2 ccm) children under that age 10 to 30 min (0 5 to 2 ccm) according to age The patients should avoid fat in diet 24 hours [illegible] The night before treatment a sal[illegible] light liquid diet is allowed In [illegible] an empty stomach followed one hour after by a dose of magnesium sulphate The patient should lie down and rest till the bowels are evacuated Then fruit juice with plenty of sugar is given fatty food and alcoholic drink should be avoided for next 24 hours The same treatment has been found to be effective in *T Solium* and T Saginata infestations

Hexylresorcinol is the drug of choice for ascaris infection and especially when hookworm infection is also present It has some value in tapeworm infections also Hexylresorcinol has been comparatively recently introduced and is as near an ideal anthelmintic as possible Little or no toxic symptoms are produced and contraindications are few It can be given while the patient is doing his ordinary work and there is no danger of cumulative toxic effects Its effectiveness against ascaris is no less than that of santonin or chenopodium and even against hookworm the only drug which excel it is tetrachlorethylene Two doses of the drug at interval of two weeks suffice to clear round worms as also many hookworms It compares favourably in the latter infection to a combination of tetrachlorethlyene and chenopodium especially when ascaris infection is co existing The second dose is only needed when the first has not entirely cleared the worms

Pills of hexylresorcinol should be put right back on the tongue and swallowed they should not be chewed as they irritate the mouth The drug should always be given on an empty stomach otherwise it loses effectiveness A preliminary saline purgative essential but the post purgative is not essential except to clear out the dead worms 24 hours after Hexylresorcinol crystoids are the convenient form for administration The dosage recommended in children is 0 1 gm per year of age up to 10 years and above that 1 0 gm

Hexylresorcinol is also effective against *Fasciolopsis buski* whipworms *tapeworms and pinworms infections* In tapeworm infection repeated doses are said to be more effective and generally three doses have to be given on alternate mornings with magnesium sulphate the night before The diet should be light and fruit juices with plenty of sugar should be given

PART III

REMEDIES USED AGAINST PROTOZOAL DISEASES

PROTOZOAL DISEASES

INTRODUCTORY AND GENERAL—CLASSIFICATION OF PROTOZOA INFESTING MAN AND ANIMAL VACCINE THERAPY IN PROTOZOAL DISEASES—DYSENTERIC DISORDERS· AMOEBIASIS (INTESTI NAL), CLINICAL ASPECTS, THE PROBLEM OF CURE, CHEMOPROPHYLAXIS—SECONDARY AMOEBIASI HEPATITIS AND HEPATIC ABSCESS, RARE AMOEBIC LESIONS—IPECACUANHA DERIVATIVES, EMETIN PHARMACOLOGICAL ACTION, EMETINE IN THERAPY, DOSAGE AND MODES OF ADMINISTRATION EMETINE BISMUTH IODIDE, MODES OF ACTION AND TOXIC EFFECTS OF EMETINE—QUINOLI DERIVATIVES CHINIOFONUM DIODOQUIN, VIOFORM AND ENTEROVIOFORM—ARSENICAL COMPOUNDS HOLARRHENA ANTIDYSENTERICA—OTHER DRUGS IN AMOEBIASIS—SUMMARY OF TREATMENT AMOEBIASIS—PALLIATIVE REMEDIES IN AMOEBIASIS PLANTAGO OVATA (ISPAGHULA), AEG MARMELOS (BAEL FRUIT), ACORUS CALAMUS

1. Introductory and General

[illegible] may be (1) sexual which is usually completed in two different hosts and (2) asexual in one host

The protozoal organisms attack animals, multiply in their bodies and product a train of symptoms which differ with different organisms The following table according to Stitt gives the systematic position of the protozoa which infest man —

(1) *Classification of Protozoa Infesting Man and Animals*

Class	Order	Genus	Species
I Sarcodina (Rhizopoda) Move usually by means of protoplasmic projections called pseudopodia and multiply by binary fissure in the active stage and by encystation	Gymnamoebida	Endamoeba	E. histolytica, E. coli, E gingivalis
		Endolimax	E nana
		Iodamoeba	I butschlii
		Dientamoeba	D fragilis
II Flagellata (Mastigophora) Move by mans of undulating membranes or flagellum, multiply by division of the body longitudinally into two	Protomonadida	Trypanosoma	T gambiense, T rhodesiense, T cruzi
		Leishmania	L donovani, L. infantum, L. braziliensis, L tropica
	Monozoa	Trichomonus	T hominis, T vaginalis
		Chilomastix	C. mesnili
		Embadomonas	E. intestinalis
		Enteromonas	E. hominis
	Diplozoa	*Giardia*	G lamblia

(1) *Classification of Protozoa*—(*Contd*)

Class	Order	Genus	Species
III Infusoria (Ciliata) Move by means of numerous fine cilia and glide about swiftly multiply by transverse division of the body into two and also produce resistant cysts	Heterotrichida	Balantidium Nyctotherus	B coli N faba
IV Sporozoa These have no motor organs they live parasitically in the cells or tissues of other animals Reproduction by spores	Coccidiida	Eimeria Isospora	E stiedae I hominis
	Haemosporidia	Plasmodium	P vivax P malariae P falciparum P ovale P knowlesi
	Sarcosporidia	Sarcocystis	S tenella

The commonest diseases which are caused by protozoal organisms in tropical climates may be grouped as follows —

(1) Amœbiasis (dysentery etc)
(2) Leishmaniasis (kala azar)
(3) Trypanosomiasis (sleeping sickness)
(4) Hæmosporidia infections (malaria)

From very early times attempts have been made to influence these diseases by drugs Countless drugs were introduced empirically from time to time for the treatment of parasitic diseases only to be discarded after more prolonged trials The work of Ehrlich opened up a new field for the scientific assessment of the value of drugs During the years that followed rapid advances were made in this field of chemotherapeutic research Helminths protozoa and spirochætes can be readily detected by direct examination by the microscope and hence the influence of drugs on these organisms has been studied in an elaborate fashion Though the mode of action of these drugs has not been clearly explained certain interesting data have been obtained Emetine and its derivatives and the cinchona alkaloids have been found to act on some protozoal organisms while compounds of arsenic antimony bismuth and aniline derivatives have a well marked toxic action on others

Specific drugs

The recognition of trypanosoma infections in experimental animals and their behaviour under the influence of drugs injected or administered otherwise has made possible the study of the mode of action of various remedies under laboratory conditions It has been found that different drugs have different degrees of lethal action on the parasites It has also been shown that although in a general way there is relationship between action of drugs *in vitro* and their activity *in vivo* yet there are many exceptions Drugs appearing strongly toxic to an organism *in vitro* may have very little or no action at all against the organism *in vivo*

During recent years certain definite advances have been made in the chemotherapeutic treatment of protozoal diseases

Classification of Drugs Acting on Protozoal Infections

(1) *Amoebiasis* and intestinal flagellate infections Ipecacuanha and its derivatives Quinoline derivatives such as chiniofon diodoquin and vioform

3

organic arsenicals such as carbarsone and stovarsol Holarrhena antidysenterica and its derivatives, etc Such drugs as *Plantago ovata* (Isabgul), *Aegle marmelos* (Bael fruit) have only palliative action

(2) *Leishmaniasis* Antimony compounds, arsenicals, Bayer 205, diamidino stilbene, etc

(3) *Trypanosomiasis* Arsenicals, Bayer 205 and Fourneau 309 (Moranyl) antimonials, bismuth compounds, quinoline derivatives, guanidine derivatives etc

(4) *Haemosporidial infections* (Malaria) Cinchona alkaloids, plasmochin, mepacrine, paludrine, etc

(2) Vaccine Therapy in Protozoal Diseases

During recent years evidence has been brought forward to show that immunity may develop in protozoal diseases, and in accordance with this hypothesis vaccines have been tried by several workers in the treatment of protozoal infections It must be pointed out, however, that in contradiction to bacterial diseases, the phenomenon of immunity in protozoal infections generally is still problematical and vaccine therapy in the latter group is yet in experimental stage.

For the rational and successful employment of vaccine therapy in infectious diseases in general three conditions have to be satisfied (1) The ætiological agent of the disease should be on ... vaccine (2) ... processes of ... part (3) the ... sufficient exp ... when employed alo ... vaccine therapy in ... ed or justification at present for the ... s except in a few conditions in which ... d The following is a brief outline o ...

Judged from ... we find that there are many technic ... out of most of the pathogenic pr ... to bacteria are rather difficult to ... that have so far been successfully ... accine production are *Leishmania* ... Others such as the trypanosomes ... *the body but* it is also not easy to obtain them in a pure state for vaccine manufacture The types of protozoal vaccine that have commonly been employed in experimental work on laboratory animals are (*a*) attenuated living organisms (*b*) virulent organisms which after inoculation are controlled by treatment and (*c*) dead or disintegrated organisms and their products For use in human beings the first two are unsuited and the third which may prove useful is not available in all cases

of
tozoa

Judged from the point of view of the second ... not appear to be any more satisfactory The chief object i ... tion of antibodies for the purpose of destroying the ... wish to ascertain before employing it whether (*a*) ... that antibodies are formed in protozoal infections and (b) if so whether these antibodies play any important part in overcoming these infections Although our knowledge of the *immunity mechanism in protozoal* infections is still imperfect there is evidence that antibodies are formed in certain protozoal diseases but in these diseases there is no certainty that the antibodies elaborated are of real value in immunity In trypanosomiasis the lytic substances ... formed are supposed to play a part in the overcoming of these infections but ... as well a ... action of ... *to protoz* ... infections

sensitiveness of the phagocytic mechanism and also upon certain non specific factors such as alterations in cell permeability variations in bio-chemical conditions and in the nature of available food supply If it is so then it is still more difficult to say how far the use of specific antigens (vaccines) and the presence of specific antibodies can be of benefit in overcoming these infections

Judged from the third and last criterion we [illegible] diseases can at best be only of limited [illegible]

Taking the evidence discussed above as a whole the manufacture and use of vaccines so far as the treatment of most protozoal diseases is concerned may justifiably be said to be a matter of pure research or academic interest The results of practical employment of vaccines in the different protozoal diseases recorded below further substantiate this view

Immunity in protozoal diseases

Oriental sore It was noticed long ago that recovery from an attack of oriental sore conferred immunity to a second attack This observation was put to practical use and individuals were inoculated with material from a sore but results were not encouraging Row (1912) tried the effect of vaccines in the treatment of cases of oriental sore and claimed that he obtained favourable results Ray employed a vaccine prepared in a different way to Row's (organisms were grown on solid media and killed by freezing and thawing) and claimed that it possessed remarkable curative properties His claim has not yet been corroborated by others

Kala-azar One attack of kala azar protected dogs and monkeys from another attack This led to attempts to treat kala azar in man with vaccine but the results obtained were unsatisfactory

Dermal leishmaniasis A vaccine was employed in dermal leishmaniasis but the res[illegible] in a certain number of selected cases was noticed, in the majority of un[illegible]

Trypanosomiasis The usefulness of vaccine in trypanosomiasis has been tested only in labo[illegible] ogical tests conducted after the use of the blood serum and complement fixa[illegible]

Plasmodium infections In the [illegible]

[illegible] beings that develops in the course of [illegible] these individuals from infection when sporozoites from mosquitoes are injected

Piroplasmosis Vaccination with the living organism followed by treatment with specific drugs has been successful in prophylaxis

Babesia infections Using a vaccine made from macerated spleen and lymphatic glands of animals infected with babesia it has been claimed that about 50% of the animals develop immunity and are resistant to re-inoculation

Conclusion

From the above [illegible] has so far yielded [illegible] laboratory animals [illegible] as a therapeutic agent has furnished neither successful nor encouraging [illegible] with [illegible] tion [illegible]

results, but at the present time their value seems to be doubtful Neither vaccines nor sera have any place in the treatment of these diseases at present.

2. Dysenteric Disorders

The term 'dysentery' is derived from Greek word meaning 'complaint of the bowel [illegible]
mucus in th[illegible]
straining and[illegible]
various groups may resemble each other in many ways [illegible] There are three main groups of dysentery —

I *Bacillary or epidemic dysentery* produced by the dysentery group of bacteria *e g*, Shiga Flexner, Sonne etc These will be discussed under Bacterial Diseases

II *Protozoal dysentery*

III *Metazoal or Helminthic dysenteries* (*Bilharzial* and *Verminous*) discussed under Helminthic disease

PROTOZOAL OR ENDEMIC DYSENTERY

Manson Bahr has classified Protozoal dysentery as follows —

(*a*) *Amoebiasis* or infection with *Entamoeba histolytica* (Schaudinn) This term includes —

1 Primary intestinal amœbiasis or amœbic dysentery
2 Secondary amœbiasis *i e*, complications, such as hepatic amœbiasis amœbic liver abscess, etc

(*b*) *Balantidiasis* or infection of the intestines with an infusorium *Balantidium coli* This is rare in man though common in animals

(*c*) *Giardiasis* or *lambliasis*, infection of the bowel with *Giardia lamblia* a protozoal flagellate

(*d*) Flagellate diarrhoea or infection with *Trichomonas hominis* and *Chilomastix mesneli* which is rather a doubtful entity

(*e*) *Coccidiosis* infection with *Isospora hominis*, a rare infection of the gut in man

(*f*) *Malarial dysentery* occuring in the course of M T infection(*P falciparum*)

(*g*) *Leishmanial* dysentery occuring in the course of kala azar

Amœbiasis or entamœbiasis includes tropical, endemic or amœbic dysentery or intestinal amœbiasis Its secondary manifestations are amœbic hepatitis and amœbic abscess of liver, lung brain, spleen and epididymus Amœbic ulceration of skin also occurs The aim of the parasite is to infect man without causing death of the host

CHAPTER I

AMŒBIASIS

(1) Amœbiasis (Intestinal)

All enicity trated hat in ontains *a thin* lution when The hree weeks and they cause new infections when *e produced in* cultures of *E histolytica* under t the cysts do not develop in the small intestine where plenty of fluid is present Dobell (1028) the escape of a single *quadrinucleate amœbae* through a minute perforation in the cyst wall No sexual phenomena have been observed during the metacystic stage

Races of E histolytica

Craig has discussed … *E histolytica* (*E dispar* … tica of varying virulence and … r to the first question is probably … the answer to the third cannot be given as the evidence is insufficient inspite of the knowledge that specific complement fixing bodies occur in the blood of animals and individuals infected with *E histolytica* Long continued infection may lead to relative immunity

Races of *E histolytica* producing small cysts have been encountered As a result of experiments designed to compare the small race with the ordinary one it was found that the small race was more difficult to cultivate and that in the culture the amœbae whether small or large were reaching the size of the amœbae in cultures of the large race

has been worked out

Non pathogenic entamœbæ occur in the human intestine *E coli* is by far the commonest organism *Endolimax nana* resembles a small *E coli* its oval cyst contains four nuclei *Iodamoeba butschlii* has a vesicular nucleus and its cysts have a signet ring like nucleus with a large and very *prominent glycogen vacuole* *Dientamoeba fragilis* shows two nuclei *E dispar* can only be differentiated from *E histolytica* by injection into the rectum of kittens

Normal habitat

amœbic dysentery or amœbic affection of the liver

In the intestines all degrees of ulceration may be present from the minimal producing … with active amœbae The symptoms … d most of the individuals suffering … are however a source of infection … fæces In only a small proportion,

Infecti ... , fæcal contamination of food a ... d remain infective in water and ... ks and rivers may be infected

The cysts when ingested pass through the stomach and excyst in the small intestines, a metacystic amœba with four nuclei emerges from each cyst After complex metacystic development eight small amœbulæ are produced from each metacystic amœba The amœbulæ grow and divide by binary fission into active trophozoites which invade tissues and produce disease in the large intestines When required conditions develop, cyst formation occurs and the cycle is repeated

Amœbic infection unlike bacillary dysentery, does not usually occur in epidemics but in form of sporadic cases Occurence of a large number of cases often means a common ... the common

fæces at room temperature they die very quickly Lowered resistance of the patient to disease is an important factor in the incidence of the disease. The disease occurs at all ages but is comparatively less frequent in children; men are more commonly affected than women Amœbiasis does not exhibit that seasonal incidence which is characteristic of bacillary dysentery, though the risk of fæcal contamination is greater in rainy season

There are 'healthy' cyst carriers who are apparently normal Such persons harbour *living entamœbae in their tissues There are also convalescent carriers* The lesions of the mucosa may be very minute and may be only visible in microscopic sections of the bowel.

intestinal protozoa in general

... there is reason ... ntries than in ... *tries*, but the ... hern countries ... œbic dysentery ... sca In India ... ay A survey ... of 12 per cent among the population but this figure is probably ...

Mature living cysts of *E histolytic* when swallowed pass through the stomach unchanged *In the small intestines* the wall of the cyst is absorbed and the young amœbae pass on with the intestinal contents into the large intestines where they establish themselves Amœbic dysentery is a disease of the large intestines, but occassionally it attacks the small intestines, the symptoms then resembling those of a bacillary infection

The young *amœbae first attack and destroy the columnar epithelium* and then pass down the crypts of *Lieberkuhn*, they penetrate the basement membrane and reach the submucosa Here they attack *the tissues by means of the powerful cytolytic* ferment which they secrete By active proliferation, nests of amœbae form which multiply rapidly with ... from the tissues The amœbae engulf red corpuscles ... ed ... ns. ... th ... a ... ges

... shape or a button hole appearance ... The smallest ulcers look like granular ... with the aid of a *magnifying* glass ... al in colour and texture Solitary ... ary black sloughs frequently project- ... sa *may be covered with a* stringy

black exudate looking like sea weed *The walls of the caecum and ascending colon may become attenuated and dilated, the portion between the ulcers may bulge like small balloons In chronic cases the wall is thickened and fibrosed and its physiological functions are interfered with* Shallow ulcers with undermined edges and brownish bases formed of granulation tissue are of bacillary origin and the infecting organism can be isolated from these Healed amoebic ulcers take the form of smooth, depressed, non pigmented scars, while those of bacillary origin are pigmented and very friable

The character of the stool depends upon the size and nature of lesions Stools are offensive when there is a lot of necrotic tissue The lesions are most extensive in the proximity of the flexures and in severe cases the mucosa of the whole of the large gut may be involved

Experimental work on cats shows that *E histolytica* first attack the large bowel especially the lower part immediately above the anal ring Amoebae enter the connective tissue or into the crypts or the lymphatic channels from here they migrate into the lymph
are the smallest and can be
testinal amoebiasis as at such
the bowel The appendix is
en there are extensive lesions
even the whole of transverse
Hæmorrhage and perforation
ccidents which may occur in
intestinal amoebiasis Localised peritoneal abscesses may be formed by walling off of the peritoneum in the neighbourhood of a perforated abscess Post mortem, few signs of toxic absorption and few visceral changes are seen

Microscopically the smaller capillaries show stasis then become thrombosed with resulting oedema and coagulation necrosis Amoebae invade the walls of the thrombosed vessels and can be seen in the coagulated blood they probably gain entrance into the portal circulation from here and so reach the liver Beyond the cellular infiltration the lymphatics
ughs and appearance of granula
brous tissue a scar of slate grey
re even in extensive ulceration is

(2) Clinical Aspects

Symptoms

E histolytica on the whole endeavours to live in harmony with the human host but acute and rapidly fatal cases may be seen As a rule the course of the disease is long drawn out and the patient though passing blood and mucus in the stools may lead an active and useful life The infection may simulate almost any gastro intestinal condition Although in acute amoebic dysentery emaciation may occur in the chronic form this is rare Death may result from perforation of ulcers or erosion of some large blood vessel in the intestinal wall

In carriers, some variations from the normal must occur The incubation period is
life unless properly and intensively treated
tion to those produced by new growths in the bowel The onset is generally gradual and progressive It often commences as mild diarrhœa which may last several days and then blood and mucus may appear in the stool In a large group it may not go beyond the stage of amoebic diarrhœa and often there is alternating diarrhœa and constipation Intense abdominal symptoms, such as those occuring in bacillary dysentery are absent There is however considerable abdominal discomfort Fever is usually absent, but rarely hectic fever occurs due to septic absorption from the ulcers In some epidemics, acute onset with fever intense abdominal pain and tenesmus have occured and the condition has been mistaken for appendicitis

The stools are more copious than in bacillary dysentery and seldom exceed twelve in 24 hours usually there are only 3 or 4 which contains dark blood and mucus resembling 'anchovy sauce'

Pain may be localised in some parts of the large intestines and is of a subjective nature It is usually confined to the sigmoid and descending colon or to the area of caecum and appendix The involvement of the cæcum [illegible] citis Pain elicited on deep pressure in [illegible] anterior superior spine of the ilium acc[illegible] significance and might be termed the an[illegible] centre of the transverse colon and may be [illegible] Pain may also be referred to the lumbar [illegible] pyelitis or renal calculus

The bowel symptoms that is diarrhœa with blood and mucus are usually quite painless in some cases the main symptom is constipation Flatulance may persist and gaseous distension of colon and caecum is a cardinal sign of the disease This may produce symptoms *of acute dyspepsia and even those of duodenal ulceration*

Palpable abdominal tumours with blood stained discharge might suggest malignant disease

Fulminating cases of amœbic dysentery are very rare and in these massive destruction of intestinal mucosa may produce septicæmia and death

Many cases with cysts in their stools do not show any gastro intestinal symptoms, some have mild symptoms to which they become accustomed and therefore they are not aware of the disease A large majority of cases of chronic amoebiasis met with in India belong to this category They do not even give a history of ever having suffered from an attack of dysentery They are in fact surprised when they are told that they have amœbiasis They are a source of danger not only to themselves but also to the community in which they live

Others suffer from attacks of slight diarrhœa or constipation indigestion distension of abdomen after meals loss of appetite, lassitude and dull aching pains in the back, extremities and lower part of the abdomen. The complexion is sallow and the face has a peculiar dull flabby and under nourished appearance The patients may be nervous and irritable Often there is mental depression. The pulse is generally of low tension irritable and may be arrhythmic On deep palpation there is tenderness of the large intestines and over the liver region Large gut may be thickened and palpable

Perforation may be fatal Hæmorrhage from a perforated artery may occur Acute amœbic hepatitis occurs in about 5 per cent of cases Sacculation of the large intestine with dilation may occur Intestinal amœbiasis and sprue often co exist Cachexia may rarely occur Prolapse of rectum is rarely seen Pericolic abscess leading to partial or complete obstruction has been met with External piles are often present Spasticity of sigmoid colon is frequently seen in intestinal amœbiasis Infection of ulcers with organisms such as streptococcus *or B coli* may produce secondary infections *Neurasthenic symptoms may be* produced and these are often referred to as 'tropical neurasthenia' *Gastric and* duodenal ulceration or diverticulitis may occur The gastric secretion is not affected Strictures of the bowel are very rare

Microscopic examination of *stools* shows *E histolytica in motile and dividing* or cystic forms the former only being present when blood and mucus are being passed. Carriers of *E histolytica* have normal stools with cysts but the large tissue invading forms which have ingested red blood cells are only rarely present It is exceptional to find the tissue-invading forms in chronic amœbic dysentery The organism is found in the blood streaked mucus and in the clots *Single amœbae or clumps may* be demonstrated. The exudate may fail to reveal the parasite In cases with secondary lesions such as liver abscess, amœbæ are usually absent in the stool In the chronic stage cysts are difficult to find at times but on other occasions they may occur in large numbers Stools should therefore, be examined for six or more consecutive days before a negative diagnosis is made, the

writer has found them after twenty negative examinations Amœbæ and cysts usually appear after a saline purgative, castor oil should be avoided as the oily droplets make examination of stools difficult The fæces should be as fresh as possible (passed immediately or not longer than one hour) especially in the acute stage as vegetative forms rapidly degenerate outside the body and die within two hours The cysts, however, remain alive and recognisable in the stool for many days sometime several weeks under ordinary conditions of moisture and temperature In trained hands positive observations may be made in 75 per cent of cases on first examination and in 90 per cent after the second examination Examination should be made on a warm stage Charcot Leyden crystals are present in 25 per cent of cases of intestinal amœbiasis but these are not pathognomonic as they occur in intestinal stasis of all forms The sigmoidoscope may reveal lesions in the rectum in 80 per cent of cases These lesions are quite distinctive and amœbæ can be demonstrated in scrapings from the ulcers In the acute stage the examination with sigmoidoscope is painless as compared with bacillary dysentery [illegible] the intervening mucosa is normal [illegible] small petechial hæmorrhages [illegible]

[illegible] dysentery the patient may remain free [illegible] signs and symptoms of disease [illegible]

[illegible]

may possibly [illegible] than in bacilla[ry] [illegible] great help an[d] [illegible]

Errors in laboratory diagnosis

The value [illegible] with typical free or encysted *E* [illegible] necessity of freshness of stools cannot be too strongly emphasised and it is advisable that stool be passed in the laboratory if possible It is a mere waste of time to examine stale stools Fæces obtained after the ingestion of oil bismuth or arsenic or after a saline purge are liable to lead to errors

(For details see Part II)

(3) The Problem of Cure

Dysentery is a clinical syndrome implying the passage of blood pus and mucus with the stool accompanied by tenesmus and the term has been loosely used even to cover the carriers where these symptoms are absent Some use the word cure in the sense that vegetative and cystic entamœbæ are [illegible] others use it to mean that the [illegible]

Criteria of cure

[illegible] days after the cessation of [illegible] as the criterion of cure and for all practical purposes this

suffices moreover, when the patients are relieved of all their symptoms they cannot be persuaded to stay in the hospital much longer The treated cases are divided into three main groups

(1) *Failure of treatment* If either vegetative or cystic forms of *E histolytica* are present, the treatment has failed

(2) *Probable cures* If the examination of six stools after cessation of treatment gives negative results the case is probably cured These cases however cannot be said to be absolutely cured but the chances are on the side of a favour able prognosis

(3) *Indeterminate cases* If however six stools have not been obtained the case is indeterminate' and the *majority of cases unfortunately* fall under this head in actual practice

It may be emphasized here that it is very difficult to prove that *E histolytica* has been eradicated after treatment even if it has entirely disappeared from the stools It is well known that both vegetative and cystic forms disappear from the stools for weeks in uncured cases after cessation of treatment and then reappear Periodic sigmoidoscopic examinations are very helpful

In experimental animals no immunity phenomena have been observed in *E histolytica* infections In man a previous cured attack does not prevent liability to a fresh attack Immunity to infection appears to be dependent upon the resisting power of the individual

According to Craig certain individuals are so resistent to infection by *E histolytica* that infection to the point of definite symptomatology is impossible and spontaneous disappearance of the parasite may eventually occur Long continued infection may lead to relative immunity so far as symptomatology is concerned as people living in regions where incidence of infections is high show little symptoms and infection is rarely encountered in them In such regions it is the new-comers who are almost always infected and show severe symptoms That human system reacts to *E histolytica* is proved by the fact that precipitins and complement fixing substance can be demonstrated in the blood Their rela tion however to immunity is not known It is possible that such organs as the liver may possess some immunity as the amœbae may be present in the liver without abscess formation

When actual symptoms of dysentery are present the amœbæ are numerous and in *full activity and are amenable to the action of emetine* The reason is that the gut in these conditions is hyperæmic and emetine circulating in the blood will hav [illegible] ment are the inde [illegible] ny drug [illegible] n [illegible] or ing and fibrosis of the gut the amœbæ are walled in and it [illegible] emetine to reach them When there is a *co existing infection* with bacillary dysentery especially of the Flexner group the contents of the gut are very acid and there emetine is not so effective

Why it is that entamœbæ cause symptoms in one individual and not in another is difficult to explain The influence of environment on the vegetative forms of *E histolytica* is an important factor the stasis of the gut contents and their [illegible] amœbæ It is possible that [illegible] ent emetine from produ

Whenever possible, examination of the ulcer with the sigmoidoscope should be done for diagnosis as well as to see the curative effect of the drug. This instrument is of great practical use in the diagnosis of the latent stages of amœbic dysentery. Ulceration may be present without producing any pain. A healed scar after treatment is a sign that the amœbic activity has disappeared, but when traces of lesions are seen in the small depressions or pits which stud the mucosa, the disease has not been eradicated

Sign copy

Diet is of great importance in the early stages of treatment of acute dysentery. Less food means more rest for the inflamed intestine, but this should not be done at the expense of the patient's strength. For the first few days it is preferable to give fluid diet such as chicken broth, rice water, egg albumin or barley water. Later, milk diluted with lime water and barley water or citrated milk may be given if curds are being formed. When this is well borne pure milk, Horlick's milk, or Benger's food may be substituted. Some patients, however, develop a distaste for milk and cannot digest it and such things as rice water (kanji), liver soup, jelly, fruit juices, etc may be given. Very strict dietary is not necessary for sub-acute and chronic cases. It is not necessary to restrict the diet of carriers during treatment, but such articles of diet as are irritating or leave a large residue e g, vegetables, hot curries etc, should be forbidden. It is advisable to stop all alcohol and also smoking during the treatment. During the convalescent stage the diet should be gradually increased, milk, puddings of sago, arrowroot, rice, cornflower, custard, etc. being given in place of milk, later lightly boiled eggs and toast butter or a little soft boiled rice, fish, and white meat should be added gradually also grapes, baked or stewed apples, banana, orange, etc

Diet in amoebia

In addition to diet restrictions, the patient should avoid chill and exposures. The patients who have suffered from amœbic dysentery, even though the infection may be eradicated, are always liable to attacks of looseness of the bowels, the gastro-intestinal tract being very susceptible to slight irritations for a long time after.

Manson-Bahr has laid down the following dietary for four weeks after active treatment

PERMITTED Porridge, eggs, fish (haddock, plaice, cod sole or whiting either boiled or fried), chicken (boiled or roasted), rabbit, game (pheasants partridges pigeons, etc), milk puddings (rice sago, semolina, ground rice) toast, rusks, or biscuits, brown bread, vita bread, vegetables (spinach, vegetable marrow cauliflower brussels sprouts, young carrots, or young turnips) stewed fruit (pears, peaches, or prunes) baked apples bananas grapes, oranges, grape fruit, plain cakes, fruit jellies, custard pudding or plain puddings. Red meat—such as underdone beef or mutton—is advocated for lunch and such dishes as tripe, brains and sweetbreads are also allowed Beverages—light wine or claret

PERMITTED Cheese new bread potatoes, fats suet puddings rich cakes, pastry of all kinds, coarse fruit and vegetables (old turnips or carrots, cabbage), pickles sardines and preserved fish. Beverages—spirits, beer or stout

Prognosis on the whole is good if the patient receives proper treatment. Even if the patient does not, the prognosis so far as danger to life is concerned, is good but so far as maintenance of general health is concerned it is not favourable. There is always the danger of hepatic abscess and other complications setting in. In the carrier cases the prognosis is very good and there is every chance of eradicating the infection if proper and persistent treatment is given. There is a chance of spontaneous recovery but without treatment the prognosis in these cases is uncertain in as much as good health cannot be insured

Prognosis

Prognosis in those suffering from repeated attacks of diarrhœa is uncertain but here also infection can be eradicated with some of the modern effective drugs.

Mortality in amœbic dysentery is stated by Craig to be over 5 per cent in epidemic in Chicago which appears to be a high figure in view of the modern effective treatment Prior to introduction of emetine treatment it is stated to have varied between 20 to 40 per cent Prognosis is less favourable in patients who have had frequent attacks of acute dysentery as it leads to a condition of chronic invalidism
days and in these the
of disease is doubtfu
when treated with emetine and aspiration When complicated with empyema it is said to be as high as 77 7 per cent Prognosis increases in gravity with the number of abscesses and patients with multiple abscesses usually end fatally even with the best of treatment it cannot be less than 25 to 30 per cent (Craig) It is therefore very important to diagnose and treat the pre suppurative stage with emetine even when operative treatment is necessary administration of emetine reduces mortality Prognosis in lung abscess is not good on account of pneumonia or empyema setting in In brain abscess it is hopeless

Amœbiasis is an important public health problem and its successful prevention and eradication depends on general sanitation pure water supply and prevention of contamination of food from flies etc Chlorination of water does not destroy *E histolytica* Care should be taken with regard to eating of raw vegetables fruits and food exposed to contamination The question of dealing with carriers is important and they should not be allowed to handle food Proper disposal of night soil and protection of water supplies against fæcal contamination is of *prime importance Most of the epidemics are water borne Carriers* should be detected and treated

(4) Chemoprophylaxis

It was found that travellers and tourists during their stay in the regions where amœbic infection was endemic sometimes contracted such infections which proved very troublesome and were difficult to eradicate Naturally the idea of using some of the amœbicidal drugs as a prophylactic against amœbic infection came up These drugs however could not be used in the case of permanent residents but may be given to people who are going to stay for a short period in an endemic area

Diodoquin and Chiniofon are the two drugs that have been used for that purpose Arsenicals although strongly amœbicidal cannot be used without

even after prolonged use.

The dosage of diodoquin recommended for prophylactic purposes is 7 tablets in a day i e 2 tablets after breakfast 2 after luncheon and 3 after dinner According to Craig even two tablets after breakfast and two after lunch are effective This should be continued for 20 days If the stay is to be prolonged the drug can further be administered after an interval of a week while if the period of stay is less the drug should be taken for 20 days without reference to date of departure Sometime 1 to 3 tablets of Chiniofon have been taken at

the onset of an attack of diarrhœa and continued as long as the symptoms persist with good result

3. Secondary Amoebiasis

Amoebic Hepatitis and liver abscess

Next to involvement of the intestines the liver is most frequently affected
n amœbiasis Acute amœbic hepatitis may occur at any time during the course
f the disease and its incidence may be about 5 per cent It may start during the
cute stages of the disease or may suddenly start during the course of a remission
The patient has acute precordial pain or a dull painful sensation over the hepatic
region made worse by movement The temperature may rise to 104°F with a
rigor and the patient has profuse sweating dicrotic pulse flushed face and furred
tongue, the liver is enlarged (3 to 4 inches below the costal margin) and is
tender, a leucocyte count of 20 000 to 30 000 is usually found Acute hepatitis
may subside in 3 or 4 days with or without any treatment or the condition may
yield rapidly to injections of emetine Amœbic hepatitis is probably due to
massive invasion of the liver with *E histolytica* and may occur years after all
the intestinal symptoms have disappeared in people living in the endemic areas

(1) Hepatitis and hepatic Abscess

Acute hepatitis

Acute hepatitis is not easy to distinguish from acute cholecystitis but in the latter
eucocytosis is not so marked Association with obstructive type of jaundice is also not
et with Sometime pain is referred to the umbilical region or the right iliac fossa resembl
g a perforated gastric ulcer or appendicitis Chronic amœbic hepatitis may be confused
th any other forms of enlargement of liver such as that resulting from cirrhosis malaria
It is often a precursor of hepatic abscess, and usually subsides with emetine therapy

Hepatic abscess

Amœbic abscess of the liver has been shown to definitely occur in intestinal amœbiasis
and absence of amœbic infection in the intestines does not rule out amœbic liver abscess
It is especially common in Europeans (2 to 5 per cent of infections) and it was much more
frequently seen in pre-emetine days Abuse of alcohol is said to be a predisposing factor

Pathology

Amœba have been found multiplying in the lumen of some of the deeper veins and
the liver is probably affected via the portal vein On account of the anastomosis of lymphatics
between the pleura and the liver the pleura may also be affected Amœbæ on reaching
the liver may not obtain a footing and may be killed if they do get a footing they break
in the liver cells, feed on them and multiply forming necrotic foci Several primary centres
may coalesce and form an abscess with cytolised liver cells in all stages of degeneration
forming a gummatous material (reddish brown liver abscess pus) this is usually bacterio-
logically sterile though it may become secondarily infected with such organisms as *B coli*
and the streptococcus Liver abscesses are usually solitary but may be multiple (in 30 per
cent of cases) The left lobe is less commonly affected but the abscess may increase and
involve the whole of the liver At any time a liver abscess may become encapsuled by
arrest of its growth the pus then becomes absorbed and becomes like thick cream cheese
in consistency Calcification may finally take place The walls of such abscesses are fibrous
and smooth but these changes only take place when amœbæ are destroyed as a result
of the treatment or some other cause An abscess may be seen externally when it is large
or multiple Local peritonitis may occur by contact

Symptomatology

The patient first feels an uneasy sensation over the liver and later there are sharp stabbing
pains radiating towards the right shoulder especially at night in abscesses of the left lobe
pain may be referred to the left shoulder joint A very tender spot may often be found
over the right rectus muscle Soon the patient gets rigors and fever the tongue becomes
furred, appetite is lost, and complexion becomes muddy The temperature is highest at
o PM and normal or even subnormal in the morning, there is profuse sweating insomnia,
restlessness and loss of weight The liver dullness may extend an inch or more above the
normal level in the nipple line deep inspiration may produce pain the spleen is not enlarged
unless malaria co-exists. There may be a pleuritic rub at the base of the right lung
decrease of breath sounds and inspiratory crepitations may be present in cases where the
ion is extensive.

The abscess may produce emaciation and death unless relieved by operation or it may burst into the right lung pleura or into a viscus and may thus discharge itself (natural cure)

Rarely symptoms may be entirely absent until the abscess bursts or it may be only detected in post mortem At other times initial fever may resemble typhoid which may later assume a quotidian or intermittent character Swelling in the epigastric or the hypogastric regions resembling tumours and even varicosity of veins in epigastric region may be seen Night sweats occur in more than 80 per cent of cases and enlargement of liver in 75 per cent Mortality used to be 50-80 per cent in old days but owing to improvement in diagonosis and treatment it has been reduced to less than 6 per cent

Liver abscess is frequently missed on account of the variety of symptoms that accompany it It may be mistaken for malaria (rigors occur) kala azar (night sweats occur) undulant fever etc It must be differentiated from gumma tubercular abscess malignant disease pyaemic gall bladder pleurisy subphrenic abscess etc Evidence of previous ulceration of the large gut shown by sigmoidoscopic examination discovery of *E histolytica* cysts in the stools leucocytosis (on an average 15,000 to 30 000) anæmia and radiological examination may be helpful The chief points in radiological examination are fixation and limitation of movements of the diaphragm on the affected side and sometime irregularity of outline and increase in size or doming of the diaphragm on the right side. The cardiophrenic angle becomes less acute

Aspiration with an exploring needle and drawing the pus makes diagnosis a certainty As the inferior vena cava lies in that region the aspiration needle should not be inserted to a greater distance than 3¼ inches from the chest wall The needle should be inserted after local anæsthesia at the most te[illegible]
there is a definite bulging in an inte[illegible]
be selected or the posterior part of th[illegible]
The needle should always be inserted
nipple in which case it will tap the
the needle is being pushed in, traction
which may be encountered The needle
liver pus is chocolate coloured and is
disintegrating leucocytes degenerating
tests are not helpful

Acute amœbic hepatitis yields very quickly to emetine injections and improvement is noticed after injection of one grain for 2 or 3 consecutive days After this the same dosage is administered as in routine anti amœbic treatment Chronic amœbic hepatitis is also amenable to anti amœbic treatment with injections of emetine or use of ipecacuanha powder The patient should be put on a light diet, and aperients especially sulphates of sodium or magnesium should be given with caution Heat should be applied to the part in form of hot fomentations and antiphlogestine or dry cupping and leeches may be applied over the affected area if there is much pain Ammonium chloride in doses of 20 gr three times a day reduces the size of the liver According to Manson Bahr pus may be absorbed after administration of EBI but this is doubted by other authorities. There is no doubt that treatment with EBI and chiniofon is distinctly helpful in preventing abscess formation

This should always be preceeded by a preliminary exploration described above A 2 per cent novocain solution is then injected and a medium or a full size needle is inserted Yellow serous fluid especially with fibrin suggests pleural exudate but it may indicate an underlying hepatic abscess Aspiration of fluid from the liver may be beneficial even if no pus is found (hepatic phlebotomy) Potains aspirator is preferred because it is safe

Surgical interference is rarely necessary in these days Transperitoneal and transpleural routes are used according to the location of the abscess and when the abscess is draining well the temperature comes down If there is another abscess it should be explored and drained Emetine should be given in form

of injections in doses of one grain each, both before and after the operation till a total of 10 to 12 grains have been given

It is now recognized that emetine therapy can by itself promote absorption of pus from a liver abscess *without* surgical interference Amœbæ it is held are killed in the liver by emetine The abscess in the active condition has a zone of hyperaemia round it and so long as amœbæ are alive the flow is from this zone towards the abscess As soon as the amœbae are destroyed by the action of emetine, the current as regards the abscess is reversed and the result is absorption and extinction of the abscess The absorption of sterile pus is in no way detrimental to the patient There is no doubt that the incidence of abscess of the liver has considerably decreased since the use of emetine in amœbic hepatitis Neither the gravity of the condition of the patient nor the size of the abscess are contraindications to treatment with emetine The disadvantage is that the absorption sometimes takes several weeks and this may weaken the patient The only indication for surgical [illegible]

[illegible]

That emetine has some stim[illegible] the fact that it is excre[illegible] conditions where functi[illegible] found emetine useful i[illegible] and chronic congestion [illegible] diseases. The cholagog[illegible] [attri]buted to emetine has not been confirmed by experiments Four injections of emetine 1 gr daily are usually effective in improving the condition whether due to amoeba or otherwise. Such doses do not produce any cumulative toxic effects

Emetine as an hepatic stimul[ant]

Emetine however, has been wrongly used in conditions simulating amœbic abscess of liver for want of proper diagnosis The writer has seen cases of chronic malaria with hepatitis given many injections of emetine because the symptoms resembled those of amœbic hepatitis. Although rigorous scientific proofs regarding the existence of primary amœbic infection of the lung brain and bladder are not forthcoming emetine injections cure these conditions when *E histolytica* is found in them. Amœbic cholecystitis has been proved by finding amœbae in the pus from the gall bladder

Emetine treatment

Emetine has a remarkable effect in acute amœbic hepatitis When the liver tissue is liquified by the action of amœbæ and when there is no bacterial infection the amœbæ are still active and are vulnerable to the action of emetine Small intra hepatic abscesses yield rapidly to emetine therapy and the necrotic tissue is absorbed.

The abscess cavity may be large and may conta[illegible] [illegible]s its walls are lined [illegible] [illegible] [conditi]on [illegible] pus is [illegible] [illegible] also the amœbæ are still vulnerable to [illegible]

In the final stages the abscess cavity is very large and the amœbæ are dead because conditions are not favourable for their multiplication Often in long standing cases secondary infection has occured and in such cases emetine is useless, the abscess has to be opened and free drainage is essential

With proper treatment with emetine the prognosis is good In abscesses which have opened into the lungs, secondary infection is bound to take place In these cases sulpha drugs or penicillin should be used

Patients who have had hepatic abscess and have been cured have lived in tropical climates for years after without any untoward effects

Pain in the hepatic region, fever and leucocytosis in patients suffering from amœbic dysentery are signs of amœbic hepatitis and beginning of abscess formation As soon as these are discovered injections of emetine should be started *(one grain daily) for not exceeding ten days* *Usually after three or four days* the symptoms completely subside if it has not gone beyond the stage of hepatitis. When abscess formation has commenced or even if an abscess pus formed, ten injections may produce resolution and absorption of the abscess If symptoms continue *surgical measures have to be adopted* *Emetine is a specific drug* in the treatment of hepatitis and there is definite evidence that the drug may cure large abscesses It is only in cases where secondary infection has taken place that surgical interference is required Here emetine therapy should be combined with aspiration and use of sulpha drugs or penicilin Radical operation is only *necessary in a small number of cases*

(2) Rare Amœbic Lesions

Lung is the next commonest organ involved by the amœbae *It may be attacked as a* result of direct extension of the abscess from the liver as the infection may be conveyed by the hepatic veins Rupture of a liver abscess is a more common source of infection which is the commonest accident occuring in 10 to 20 per cent cases of liver abscess

The formation of the abscess is preceeded by development of pleurisy, shown by pain, irritable cough and quick shallow respiration As the abscess advances signs of consolidation become apparent

[illegible] onchus In the latter cases, The patient may succumb after discharge of the pus of the liver

Brain Abscess is a fatal complication of amœbic infection and is seen most frequently among Europeans Male adults between 20 to 40 years are more commonly affected Generally the victim has had lung or liver abcess which may have become cured even months *before The abscess is usually single developing in one of the cerebral hemispheres*

Pathology is the same as in the liver abscess the contents being generally bacteriologically sterile and necrosed brain tissue attached to the thrombosed vessels containing large numbers of amœbae Meningitis is generally absent

[illegible] hose of a

tion of stools plus [illegible]
in arriving at the cor[illegible]
[illegible] on and drainage of abscess

Chronic adhesive peritonitis localized in patches is seen as a rule in old standing cases Acute peritonitis which is a fatal complication may sometimes be seen as a result of perforation of a deep ulcer or rupture of a liver abscess Treatment consists of rest, application of heat and surgical measures

Appendicitis may often occur as a result of extension of ulceration from the caecum Definite diagnosis is however often difficult

Other complications still rarely met with are splenic abscess ovarian abscess cystitis, parotitis fistula and intestinal heamorrhage *The last named may be severe* and recurrent d[illegible] to liver abscess or independent of that from the intestines originally

Appendicitis occurring in the course of amœbic infection is often controlled by injections of emetine and chiniofon Invasion of appendix means that the caecum is involved and operative procedure in these cases leads to complication Appendicostomy and cæcostomy once recommended are valueless

CHEMO-THERAPY OF AMŒBIASIS

4 Ipecacuanha Derivatives

Historical

Ipecacuanha or 'Brazil root' was used in Brazil as a remedy for dysentery many centuries ago In 1684 it was brought to Europe and an account of its antidysenteric properties was published The remedy soon came into use generally

The powdered bark was given in 2 drachm doses with tincture of opium to prevent nausea and vomiting and beneficial results were obtained in dysentery tropical hepatitis and other conditions The value of the remedy as a cure for dysentery became gradually established and in 1912 *emetine* the alkaloidal active principle came into use instead of the root

The root is obtained from two species of Cephaelis belonging to the natural order Rubiaceæ (1) *C ipecacuanha* or the Rio ipecac (also known as *Psychotria ipecacuanha*) This is the only form recognised by the British Pharmacopœia (2) *C acuminata* or Carthagena ipecacuanha has a thicker root its annulations are less marked and it is cheaper The plant grows about 30 centimetres in height and is found in most parts of Brazil

Plantations were successfully started in India in the Nilgiris and at Mungpoo near Darjeeling The British Pharmacopoeia (1932) required that the root should not contain less than 2 0 per cent of the alkaloids The United States Pharmacopoeia allows both *Cephaelis ipecacuanha* (Rio) and *C acuminata* (Carthagena) if yielding not less than 2 per cent of ether soluble alkaloids

Characters of the root

From the slender root and prostrated stem roots are given off at intervals, some of [illegible] per cent of total alkaloids

Ipecacuanha stem has often been found mixed up with the root and much of the drug that is imported is a mixture of the two It contains 0 97 to 1 8 per cent of the total alkaloids the yield being lower than that of the root

The rhizome of a small monocotyledon plant *Cryptocoryne spiralis* (Tamil *Athi Vadayam*) has been exported from Southern India (Madras) the root of *Psychotria emetica* or the greater striated ipecacuanha the roots of *Richardsonia* the root of *Ionidium ipecacuanha* *Trinidad ipecacuanha* which is the rhizome and root of *Asclepias curassavica* *Narrgamia alata* (*tin pani* or *tittel*) grows in Western India are some of the [illegible] and adulterants

Test for emetine

The following test for emetine is useful for distinguishing roots which contain the alkaloid from numerous substitutes

Half a gm of the powdered root is mixed with 20 ccm of strong hydrochloric acid and 5 ccm of water and filtered To 2 ccm of filtrate 0 01 gm of potassium chlorate is added if emetine is present the liquid assumes a yellow colour changing to red in the course of an hour

Chemistry of the alkaloids

In 1817 Pelletier isolated the alkaloid emetine in collaboration with Magendie its physiological action was determined and in 1829 it was first used in the treatment of dysentery The discovery of emetine was quickly followed by the isolation of several other important alkaloids strychnine quinine and veratrine Pelletier's emetine contained the total alkaloids of ipecacuanha and this name continued till 1894 when it was shown that it consisted of two alkaloids namely *emetine* and *cephaeline* Subsequently the presence of

a third alkaloid psychotrine was demonstrated which occurs only in small quantities These three alkaloids are chemically closely related

n
ers
loids

Emetine is a white amorphous substance which darkens on exposure to light, gradually assuming a yellow colc
acetate is amorphous
and is easily soluble in
the latter substance is f
fore appear to be relate
have been shown to have a well marked toxic effect on protozoa Emetine is methyl cephæline iso emetine is probably a stereo isomeride of emetine, but attempts to convert one to the other have so far been unsuccessful Iso emetine is considered by some to be a methyl ester of iso cephæline Iso emetine is non emetic and comparatively non toxic, it has little effect in *E histolytica* infections

Cephaeline is a crystalline alkaloid less soluble than emetine, it is soluble in alkaline *solutions and darkens on exposure By methylation it is converted into emetine Cephæline* hydrochloride in doses of 1/12 to 1/6 grain is said to be a more powerful emetic than emetine

Psychotrine is related to cephæline but has 2 atoms of hydrogen less It is the least toxic of the three alkaloids and has a doubtful therapeutic effect in amœbic infection On reduction psychotrine yields a mixture of cephæline and iso cephæline, these on methylation *yield emetine and iso emetine respectively*

Pyman (1917) isolated two new alkaloids—*O methyl psychotrine* and *emetamine* from Ipecacuanha roots and the presence of traces of two other alkaloids are also discussed by him The former two alkaloids are closely related to psychotrine and emetine respectively

Besides the three main alkaloids there is also another constituent, ipecacuanhic acid which at one time was considered to be responsible for the action of ipecacuanha in dysentery

The relative amounts of emetine in ipecacuanha from various sources are as following —

Brazilian root	Total alkaloids 2 7 per cent emetine 1 35 per cent
Brazilian stem	Total alkaloids 1 80 per cent, emetine 1 18 per cent
Columbian root	Total alkaloids 2 20 per cent emetine 0 89 per cent
Indian root	Total alkaloids 1 98 per cent, emetine 1 39 per cent

A crystalline glucoside ipecacuanhin has also been found in the root

(1) Emetine

(a) Pharmacological Action

Vedder (1911) found that emetine in dilution of 1 in 100 000 killed living amœbæ in broth cultures and pointed out that 1 in 10 000 dilutions killed *E histolytica* in pieces of mucus in stools while 1 in 100 000 solution rendered them quite inactive in 3 minutes Emetine was also said to be lethal to free living amœbæ in dilutions up to 1 in 200 000 if the exposure was sufficiently long *Entamoeba gingivalis is paralysed in culture by a 0 25 per* ... emetine hydrochloride
Dobell (1917)
olytica obtained
iction is weak
the vegetative
alkaloids on
ibstances tested
owed to act for
ltures in fluid
e met with in
E histolytica
n was not too
hopra and his
lity and were
was *alkaline*

eventually killed by the ac

Local action

The drug is a local irritant Applied to the skin in the form of liniment it produces redness and itching, 1 in 500 solution causes marked irritation of the mucous surfaces Some individuals are extremely sensitive to these effects and in them, urticaria and dermatitis may be produced by systemic administration of emetine Application of a 1.0 per cent solution to the abraded skin may produce a weal When it comes in contact with the cornea it sets up a painful keratitis Subcutaneous or intramuscular injections cause œdema and hyperæmia of tissues and extensive capillary hæmorrhages in the muscle fibres round the site of injection Unlike the cinchona alkaloids, no necrosis of tissues is observed and the action appears to be mainly on the walls of the capillaries and arterioles A violent irritation of the bowels can be set up by irrigation with a 1 in 10,000 solution of emetine hydrochloride Half a grain taken by the mouth produces nausea quickly followed by vomiting in about an hour, an hour later loose stools are passed accompanied by griping Much larger doses than can be borne by the mouth are tolerated by injection without producing nausea vomiting and diarrhœa the effect would therefore seem to be purely local

Gastro-intestinal tract

[illegible] ...ine inhibits the action of [illegible] ...r stimulated by concentra[illegible] Proteolytic and lipolytic [illegible] dilutions accelerate these [illegible] what inhibitory Emetine increases the tone of the non striped muscle of the gastro-intestinal tract, the movements of the gut are stimulated the effect being more marked as one passes downward from the stomach to the colon It was also shown that the action was on the musculature directly and not through the nervous mechanism Emetic effects of emetine are due to reflexes and central stimulation

After injection emetine can be detected in the stomach and intestines Large doses of emetine given by injection cause swelling and congestion of the mucous membrane of the whole of the gastro intestinal tract, which is often covered with mucopurulent secretion or studded with ecchymoses In the dog ulceration of the gut has been produced by giving emetine subcutaneously

Action on circulatory system

On the heart of both [illegible] irregular, auricular and ventricular dissociation may be produced and death may occur from ventricular fibrillation, the heart stopping in diastole In animals intravenous injections of large doses produce a marked fall of blood pressure, after small doses the pressure [illegible] is due partly to the direct toxic action [illegible] is an important factor especially after [illegible] blood pressure to the extent of about [illegible] after repeated doses by other routes [illegible] ...ressible) and cardiac irregularities of various types are seen after a series of injections of this alkaloid The isolated heart is slowed and weakened by both emetine and cephæline and it finally stops in diastole

Respiratory system

There is some depression of the respiration after subcutaneous injections of the alkaloid but after intravenous injections the respiratory centre is stimulated and the frequency and the depth of the respiratory movements are increased Small doses increase the secretion of the respiratory passages and thus act as an expectorant To this is added a slight relaxation of bronchial musculature which makes the removal of mucus easier If toxic doses are given they have a decided tendency to cause pulmonary congestion or hæmorrhagic pneumonic consolidation

Nervous system

In the frog emetine causes a slowly advancing central paralysis In mammals neuritis is produced and there is general depression of this system giving rise to lethargy The nerve cells especially those of the anterior cornua are damaged first and then the fibres degenerate, there is evidence that the motor fibres are specially picked out Emetine has a powerful mental depressant action in man Painful neuritis somewhat similar to that produced by alcohol has been observed

Emetine is said to produce stimulation of the uterine movements but in dilutions such as those occuring in the body after its administration it has little or no effect

Absorption and excretion

Emetine and the allied alkaloids are rapidly absorbed from the mucous membrane and the subcutaneous tissues and are eliminated by the gastro-intestinal tract and by the kidneys Elimination of emetine by these routes is demonstrated by the effect the drug

produces in urinary and intestinal schistosomiasis A part of the drug appears to be excreted by the bile which probably accounts for its curative effect in hepatic schistosomiasis and liver flukes

Excretion by the kidneys is discontinuous and prolonged The drug appears in the urine 20 to 40 minutes after hypodermic injection of a therapeutic dose, but during the course of treatment not more than one sixth of the drug is excreted by this route Elimination proceeds by fits and *starts active periods* alternating with periods when little or none is found in the urine The elimination in patients who have received 0 15 to 0.58 gm in 3 to 6 days may last for 5 to 9 weeks showing that it forms deposits in the body In some cases the drug appears to have *been retained for* periods ranging from three months to a year Large doses irritate and produce inflammation and albuminuria together with chloride and nitrogen retention The excretion of uric acid is increased by emetine as it is by other gastro intestinal irritants

By subcutaneous [illegible]
per kilo body weig [illegible]
to 0 210 gm for a [illegible]
1 grain is well wi [illegible]
to 12 to 15

With large doses the changes produced in the tissues are of an acute nature, and *immediate death* within 24 hours may be produced with one single large dose Doses of 0 05 to 0.075 gm per kilo in dogs and 0 02 to 0 15 gm per kilo in rabbits guinea pigs rats etc are rapidly fatal There is probably no threshold of safety when the drug is taken continuously

The toxic range of emetine for all larger mammals is 15 to 20 mgm per kilo of body *weight In man it is inadvisable* to give more than 1 mgm per kilogram of body weight or a total of 10 mgm per kilogram Emetine attacks all tissues and therefore is a general protoplasmic poison change in the kidney [illegible]
showing hyperaem [illegible]
show any detectab [illegible]
degeneration The [illegible]
the anterior horn cells Chopra Gupta and Roy (1935) show that intravenous injections of emetine (1 mg per kilo) in Belgian hares decrease the iodine content of the thyroid and fall in adrenaline content of the adrenals This latter may account for the fall in blood pressure

The physiological actions of emetine and cephæline are very similar It has been shown that cephæline is more irritant and about twice as toxic and emetic as emetine, their parasiticidal action on the entamœba is about equal It is generally stated that emetine has a stronger expectorant action and is a stronger nauseant than cephæline, its depressant action on the heart and its irritant action on the kidneys are more marked Psychotrine is much less toxic but is likewise less parasiticidal Ipecacuanhic acid ipecacuanhin and various cephæline esters are more or less inert

(b) Emetine in therapy

Ipecacuanha has long been known as *Radix antidysenterica* One of the chief uses of ipecacuanha is in the treatment of amœbic dysentery and though emetine has largely replaced the powdered root, the latter is sometimes employed

powders were also used with keratin or salol coating which prevented the drug being dissolved in the stomach and allowed it to pass on to the duodenum setting free the alkaloids in the intestines These methods have now been superseded by the introduction of alkaloid emetine

Rogers (1913) started hypodermic injections of emetine as a routine treatment of dysentery Trials were initiated on a large scale and it was found that though almost a specific for acute amœbic dysentery, it had little effect on the bacillary form The oral administration of the powdered root was combined

with emetine injections as it was thought that by this method the bowel could be thoroughly permeated with the alkaloid

It may be said that both emetine and cephæline, when given in adequate doses produce a prompt disappearance of all the clinical symptoms of an acute infection with *E. histolytica* and often a permanent disappearance of this organism from the stools When given by the mouth however they produce nausea and vomiting and are often not retained Emetine has therefore to be administered in the form of injections and it preferably should be given intramuscularly on account of the tendency it has to produce local inflammations and hæmorrhages after hypodermic injections

Effects

According to Knowles (1928) the general consensus of opinion appears to be —(*a*) that emetine injections are by far the most satisfactory immediate line of treatment of amœbic dysentery but (*b*) that emetine therapy is generally a failure in the treatment of the carrier condition It has been shown that primary malaria as therapeutically introduced in the treatment of general paralysis of the insane is a disease which is readily amenable to quinine treatment only a few days of quinine treatment are necessary to effect a cure without relapses On the other hand the experience of all workers in the tropics is that established and relapsing malaria is very difficult to eradicate Possibly a similar state of affairs exists with regard to amœbic infection of the gut the prospects of eradicating the infection by emetine therapy may be much better in patients seen when suffering from the first attack of amœbic dysentery than in cases where the infection has become chronic and is well established In a series of 32 acute and chronic dysentery cases which had 6 to 9 grains emetine by daily injections of 1 grain each the ratio of probable cures to failures worked out as 1 17 The cost of treatment roughly estimated was 2 to 3 rupees per head These results are similar to those obtained by other workers Emetine injections undoubtedly cure an infection with *E. histolytica* and the alkaloid is more effective in acute amœbic dysentery than in cases of chronic amœbic colitis. In the majority of chronic infections however the injections do no more than clear up the symptoms and these patients generally become carriers

Rogers (1929) recommended daily injection of 1 grain for not more than seven or eight days He followed the treatment by 20 to 30 grain of ipecacuanha with 10 grains of tannic acid (to lessen the danger of vomiting) and a drachm of mucilage in one ounce of water to be taken last thing at night before going to bed, and repeated each night for a week By this method the organisms in the tissues as well as those in the bowels are acted upon by the drug

Emetine and bismuth

Deek's treatment consists in giving emetine injections combined with large doses (100 gr) of bismuth subnitrate orally Knowles (1928) analysed a series of 55 cases treated with daily injections of emetine combined with one drachm of bismuth carbonate by the mouth every day The patients were suffering both from acute and chronic symptoms the majority belonging to the latter class The ratio of probable cures to failures in this series was 1 18 These results are not encouraging but there appears to be little doubt that bismuth treatment in combination with emetine injections from the clinical point of view at any rate gives good results The results so far as eradication of the infection is concerned are disappointing

Emetine injections have also been used in combination with such other drugs as *diarrhena antidysenterica* bark yatren stovarsol etc

Treatment of acute cases

Acute and sub acute amoebic dysentery The following procedure for treatment of such cases has been recommended by Acton and Knowles —The patient is kept strictly in bed and made to use the bed pan A saline purgative is given in the morning to flush the colon some prefer to give an initial dose of castor oil or castor oil combined with opium (castor oil ½ oz or 15 ccm tincture of opium 15 minims) The diet should be light chiefly milk or boiled fish Emetine injections are either given alone or combined with bismuth by the mouth 1 to 2 drachms of bismuth carbonate is given every four hours in half a glassful of water during the day, with the object of decreasing the acidity of colon and increasing the alkalinity of the portal blood Two and a half hours after the first dose of bismuth an injection of 1 grain of emetine hydrochloride is given in the morning of the injection is important as it has been shown that emetine acts best in an alkaline substrate and that the alkalinity in the portal vein rises about that time This treatment is carried on for nine consecutive days For the next

three days emetine and bismuth are suspended and only a saline purgative is given The complete treatment with saline, bismuth and emetine is again repeated for 3 to 6 days The stools should then be examined for at least 6 consecutive days, preferably 8 or more This is not always possible for the patient thinks he is cured as soon as the symptoms abate and leaves the hospital

cutaneously in 1 grain doses daily for six consecutive days After an interval of three days, a second series of three injections are given in daily doses of 1 grain Bismuth carbonate in one to two drachm doses thrice daily is given throughout the course

In acute cases with severe pain and tenesmus give a hypodermic injection of 1/6 grain of morphia, or a small enema of opium and starch (tinct opii 40 minims or 2 5 ccm, mucilage of starch 1 oz or 30 ccm) Hot applications to the abdomen such as turpentine stupes, or poultices consisting of linseed meal with a little mustard are soothing The patient should be kept warm

Emetine in relapsing and chronic dysentery Chronic and relapsing amœbic dysentery is one of the common diseases of the tropics and one of the most difficult to treat ... amœbiasis
as after injection ... estroy
most of the amœb ... actory
and a large numbe ... third
of the cases, one third apparently improve and in the remaining one third the drug has no effect at all

The reason for this failure in some cases is the fact that, although emetine acts on the amœbæ lodged in the tissues of the intestinal wall, it is said to have no effect on the parasites in the lumen of the gut It is known that non pathogenic amœbæ s ... membrane and possibly *E hist*
in the tissues
to the liver where they set up hepatitis and abscesses ... organisms are only reached by emetine through the blood stream Unfortunately in long standing cases fibrosis is set ... thus prevent ing the access to the parasites of ... Entamœbæ lying in the necrotic or fibrotic t ... hus liable to escape the action of emetine This is the reason why many chronic cases are not amenable to treatment The second factor is the infection of the ulcers with *B coli* and other intestinal bacteria which further promote these pathological changes and lead to the chronicity of the lesions thus hindering the curative action of emetine Cases of bacillary dysentery both acute and chronic super imposed on a carrier condition of amœbic dysentery commonly occur in India

Briefly the difficulty of curing chronic amœbic dysentery is due to four *factors* —

(*a*) Emetine is a toxic drug and it is not possible to give it in sufficient amounts and over sufficiently prolonged periods to destroy all the *parasites* Chronic infections are resistant to treatment though relief of symptoms occurs in the majority of cases (*b*) Emetine cannot be brought into *contact* with amœbæ deeply seated in the ulcers by colonic irrigation (*c*) The presence of

secondary bacterial infection is an additional factor in preventing cure When amœbic and bacillary dysentery especially of the Flexner type co-exist, the reaction of the gut becomes very acid and emetine cannot exert its full therapeutic activity In bacillary dysentery (Shiga type) the reaction of the gut may be alkaline to litmus (pH 8 11), in the amœbic form the pH of the stools is 6 3 It is found that when the pH of the contents of the gut is 7 0 the amœbæ are dead or dying, cyst formation occurs when the pH of the contents is 7.24, Charcot Leyden crystals are passed at 6 96 The acid reaction hinders emetine which acts better in an alkaline medium Attempts at markedly raising the alkalinity of the contents of the large intestine by giving alkalies by the mouth have not met with much success The drugs which decrease the acidity of the contents of the large intestine are compounds of bismuth preferably bismuth carbonate which act by fixing the acids present

If energetic treatment is not started in the early stages before extensive destruction of tissues has taken place relapses are almost certain to occur There is little doubt that the secondary bacterial infections probably account for most of the cases of failure with emetine Resistant chronic cases of amœbic dysentery are sometime benefited with vaccine made from such organisms as streptococci dysentery bacilli etc, previous to emetine injections Emetine is much more efficacious in the early than in the later stages of dysentery The drug is not active against the encysted amœbæ which though themselves quite harmless indicate active vegetative forms in the tissues In cases of relapse a course of emetine bismuth iodide 3 grains daily for 12 days may bring about a cure Dobell and co-workers recommend a double course of this drug—3 grains (0 2 gm) daily for 24 consecutive days but in the writer s experience in India very few persons can tolerate such large doses

Treatment relapses

In the Carmichael Hospital for Tropical Diseases Calcutta a course of 1grain of emetine daily for nine days was successful in curing a number of chronic cases of amœbic dysentery The better method is combined treatment with Emetine hydrochloride by injection and emetine bismuth iodide by the mouth Emetine hydrochloride is given in one grain doses with emetine bismuth iodide 2 grains daily for 6 to 9 days Even this proved a failure in a large percentage of cases It has been shown that emetine fails to prevent cyst formation and encysted parasites remain in the gut for long periods

In a large number of cases the infection is not eradicated and often the cure s only an apparent one cysts and Charcot Leyden crystals being present in the tools When infection is not eradicated the patient may suffer now and then rom attacks of amœbic diarrhœa or he may have constipation alternating with eriods when he passes blood and mucus with stools A patient in the carrier ondition may at any time develop acute amœbic dysentery An infected person equently suffers from periodic attacks of acute amœbic dysentery when the ge tissue-invading forms of *E histolytica* are present in the stool Between attacks when acute symptoms have abated the carrier condition is maintained such cases the courses of both emetine and emetine bismuth iodide may have e repeated after a suitable interval allowing for all the emetine to be excreted ch usually takes 1 to 2 months after a course Even then eradication of disease ot ensured The drug treatment of amœbic dysentery should be controlled rever possible by sigmoidoscopic in addition to microscopic examina (See Part II)

Uncured cases and Carriers

Autopsies carried out on amœbic dysentery cases show evidence of the healing

power of emetine on amœbic ulcers In the majority of cases a 9 to 10 days course of emetine is sufficient to give relief and produce healing of the ulcers

There is no doubt that patients passing *E histolytica* cysts especially those who show thickening and tenderness of the cæcum as a *result of repeated attacks* should be submitted to repeated treatment with drugs because they have active amœbic lesions as can be demonstrated by the sigmoidoscope Due care should be taken regarding the disposal of their fæces to prevent the spread of infection.

to its action for a long time (Manson Bahr) Increased resistence of amœba in culture to emetine has been demonstrated

Emetine rapidly produces amelioration of symptoms of amœbic dysentery *e g* diarrhœa tenesmus etc, *but its curative action in subacute and chronic* cases is doubtful Careful investigations have shown that it cures only a small proportion of cases The motile and cystic forms disappear from the stools during the course of emetine treatment but they often reappear later The drug should therefore be used in daily injections of one grain each till acute symptoms have disappeared For this purpose usually 4 to 8 injections are required and more than ten injections should never be given Injections may be preferably combined with alkalies given a couple of hours before the injection, or bismuth carbonate may be given 2 or 3 times a day in doses of 1 to 2 drams

If after that amœba are found in the stool treatment with chiniofon or carbarsone or kurchi alkaloids should be given

The patient should be strictly confined to bed when emetine treatment is being given

Emetine should never be used in the treatment of chronic relapsing form *of amœbiasis except a few injections to control the troublesome symptoms* in the acute stage It is a toxic drug with a cumulative action and more then ten injections should never be given in a course The course should not be repeated in less than three months

(c) Dosage and Modes of Administration

The treatment of intestinal amœbiasis with emetine must be continuous if it is to be efficacious It must be given for a sufficient period and the dosage *should be adequate* Intermittent treatment with small doses or only for a few days may relieve acute symptoms but will not eradicate infection this may lead to a chronic condition which is very difficult to cure On the other hand it should be remembered that emetine is a highly toxic substance and if given in large quantities it may produce severe diarrhœa heart trouble great prostration and even collapse and death The consensus of opinion at the present time is that under no circumstances should more than ten to twelve injections of one grain each daily be *given in one course* as they are almost certain to produce toxic symptoms In the majority of cases 9 injections suffice. The total amount of *emetine in* one course should never exceed 0 01 gm per kilo body weight The course can however be safely repeated after an interval of 3 to 4 months For 6 months old infants a dose of 0 01-0 02 gm for one-year old 0 03 0 05gm total quantity up to 0 12 gm for yet older infants up to *0 15 gm by injection* It should be given with great caution

Prolonged administration of relatively small doses of emetine is more to be feared than a few heroic doses and the immediate toxic effects of the drug are less dangerous than those due to cumulative action. The use of larger doses on alternate days has therefore been suggested as this would enable the system to recover from the toxic effects of one dose before the next is given and thus make it possible to avoid further doses as soon as the earliest signs of cumulative action are recognised. In sufficient dosage with emetine—less than one grain a day in adults—is liable to produce emetine—resistant amoebae.

By mouth. Oral administration of ipecacuanha powder was recommended in old days to follow the course of emetine injections. 20 to 30 grains of the powder were given with 10 grains of tannic acid in a drachm of mucilage and an ounce of water three hours after a light meal and before retiring. This was repeated every night for one week. The usual practice was to begin with a larger dose such as 30 to 40 grains (2 to 2.7 gm) then to decrease it nightly by grains until a 5 grain dose was reached which was continued for a week or for if necessary. As a rule nausea and vomiting were constant accompaniments. About the middle of the course diarrhoea with canary yellow coloured stools appeared and this was looked upon as a favourable sign. In acute cases blood and mucus rapidly disappear and after the course the stool becomes normal. As the root powder contains many superfluous ingredients and is as irritant as emetine it has now a-days been superseded by the pure alkaloid.

Mode of administration

Emetine hydrochloride given by mouth is absorbed from the gut. Various devices have been adopted to reduce or abolish its nauseating or emetic effects. Unfortunately these have never succeeded without at the same time diminishing or annulling its therapeutic action. Pills and tablets coated with keratin stearin salol or other insoluble substances usually minimise the nauseating effects of emetine but these may not dissolve in the gut and therefore produce no therapeutic effect. The best method of giving emetine by the mouth is as emetine-bismuth iodide.

Oral administration

Emetine has been administered in various ways the object being to hurry its passage through the stomach so that the nauseating and emetic action of the alkaloid is avoided. Fuller's earth adsorbate or alkresta tablets have been recommended by some. Enteric sealed tablets containing 1/3 gr emetine hydrochloride have been prepared by Lilly & Co under the name of Enseals. These are designed to resist digestion for 3 to 4 hours and have given good results. Keratin coated tablets have to be used at night before going to bed the same precautions being taken as in the case of ipecacuanha treatment. Sometimes a certain amount of tolerance develops—the patient retaining the drug after rejecting it for the first 2 or 3 days. 10 to 15 minims of tincture of opium administered previously may diminish or abolish vomiting. As a rule in acute cases where the patients have to be kept in bed injections are the best; in chronic cases with slight local lesions the oral method may be employed. Administration of ipecacuanha direct into the duodenum by catheter has been tried.

Good results are said to have been obtained by enemata of 4 to 8 gm of ipecacuanha powder suspended in a pint and a half of water. Colonic irrigations of 0.1 gm of emetine in 1,000 ccm of water or saline have been employed but they are very irritating and painful. This method therefore is not recommended.

Rectal administration

Emetine is given either subcutaneously or intramuscularly. The drug is apt to cause an eczematous condition of the skin if subcutaneous injections are

Subcutaneous and intramuscular routes

repeated in a limited area Any source of focal sepsis should be eliminated as otherwise a fixation abscess may form Deep subcutaneous injection is well tolerated is less painful and is the method of choice

The drug also is less irritant and painful when given by the intramuscular route owing to smaller number of sensory nerve endings there Acton and Chopra (1924) showed that emetine injections in rabbits produced œdema and congestion of the tissues at the site of injection and extensive petechial hæmorrhages but no necrosis Some individuals develop an idiosyncracy towards the drug a considerable amount of pain and stiffness being caused and even abscess formation may occur

The symptoms last for several days and even when injections are given into the loose cellular tissue of the abdominal wall considerable redness and small hæmorrhages are found at the site of injection in spite of all precautions to secure proper sterilization of the skin and needle while other patients under the same conditions develop no trouble whatsoever Pain caused by emetine is diminished by dissolving it in a 1 0 per cent solution of carbolic acid

The intravenous route was rarely employed formerly but it has been used recently As early as 1913 intravenous injections of emetine were tried but toxic symptoms were not uncommon, these consisted of dyspnœa vomiting diarrhœa very slow pulse unconsciousness and muscular paralysis Emetine by the intravenous route has been advised in the treatment of severe cases of amœbiasis beginning with 0 03 to 0 05 gm on the first day and reaching a maximum of 0 1 gm on the fourth day, a total of from 0 5 to 0 6 gm of emetine being given in 10 days

The drug when given by this route should be well diluted and administered very slowly The dose should not exceed 1/4 to 1 grain (0 015 gm) dissolved in at least 10 to 20 ccm of sterile saline a total of 6 to 9 injections being given It is advisable to have an ampoule of adrenalin ready so that it can be given at once if there are signs of vasomotor paralysis *Intravenous injections are likely* to be followed by nausea and vomiting which may supervene ½ to 1 hour after administration The results are said to be rapid and striking and superior to *those from intramuscular or subcutaneous injections* In the writer s experience intravenous injections did not give any better results than subcutaneous and intramuscular injections Intravenous injections undoubtedly throw more strain on the heart and are not recommended

(2) Compounds of Ipecacuanha and Emetine

As emetine when given by the mouth produces vomiting so certain insoluble preparations which pass through the stomach unchanged without liberation of the alkaloid have been introduced

(a) Emetine adsorbate or Alkresta Ipecac (Lilly & Co)

Alkresta ipecac is the trade name given to an adsorption compound of the total alkaloids of [illegible] cate (Fuller's earth) It is made up in [illegible] lkaloids of 10 grains of ipecacuanha [illegible] etine is that it passes through the stomach unchanged and the alkaloid is liberated in the alkaline intestinal contents Knowles (1928) in a series of 7 cases found alkresta on the whole unsatisfactory

(b) Emetine Bismuth Iodide

Emetine bismuthous-iodide (EBI) Dose 3 grains (0 2 gm) containing approximately 1 *grain* (0 06 gm) of emetine

Du Mez (1911) manufactured emetine-mercurous-iodide and emetine bismuthous-iodide and suggested, as results of his experiments on dogs, that

believed to reinforce the action of emetine

It is believed that after administration of EBI, emetine is liberated from the compound on the surface of the mucous membrane of the gut, the insoluble bismuth salt being converted into sulphide after going through the pylorus. This reaction is probably slow and spreads over the mucous membrane. The underlying principle is that the drug decomposes in the large intestines and liberates "nascent emetine" which is very active against the amœba.

Before administering EBI, the patient should be strictly confined to bed, as unless rest is enforced, vomiting is certain to occur. Besides this, diarrhœa which invariably follows its administration, starts, and there is also danger of heart trouble. A preliminary dose of castor oil, one ounce, and tincture of opium 15 minims, is advisable. It is better to start with one grain doses and

in a course

to Manson

d doses not

It is advisable to give the double iodide as a loose powder in a hard gelatine capsule known as 'slipules' or paper cachet. It should not be given in hard or compressed tablets or mixed with insoluble excipients such as vaseline, soap, stearin, etc., nor should it be coated with keratin, salol or other more or less insoluble substances.

If a full dose of three grains is to be given it is better to give it in one capsule. Experience has shown that unless properly protected it is liable to be dissolved in the stomach giving rise to the usual irritant symptoms of emetine. Even keratin coating was found to be uncertain as nausea and vomiting were produce

readily

(0 2 gm

the ave

is the s

can rarely stand more than 2 grains daily. Some prefer to give the drug in cachets of one grain each three times a day until 36 grains (2 4 gm) have been given; larger doses very often are not tolerated.

Vomiting when it occurs does not come on as a rule until some time after the dose, indicating the probable liberation of emetine from the intestine and not from the stomach. It is recommended by some authorities that the dose be given after a full meal when the stomach contents would certainly be acid, and on the whole, administered in this way, the drug is well tolerated.

Others prefer to give it on an empty stomach, and are of opinion that given in this way it causes less nausea. The dose should be given at night when the

patient is in bed and resting quietly preferably with a cup of hot tea or arrowroot. The patient should endeavour to sleep and the saliva should be wiped from the mouth or expectorated and *not swallowed*. *In many cases there is vomiting on the first night* but this does not matter if the powder is not rejected on the second night there is usually little or no vomiting. Throughout the course there is a tendency to slight vomiting in many patients though a certain amount of tolerance does undoubtedly develop for the drug. If nausea or vomiting becomes troublesome it is necessary to give 15 minims (1 0 ccm) of tincture of opium or chlorodyne or omnopon 1/6 of a grain half an hour before each dose. Hot applications in the form of a terpentine stupe or a mustard plaster to the epigastrium may also help. To obtain s...
dose and intermission or shortening of t
and treatment should only be stopped if
supervenes. Bradycardia with nausea and low blood pressure is an indication of intolerance to the drug. Emulsions of emetine bismuth iodide in 1 ounce of liquid paraffin have been tried and are said to have given good results

As the treatment of t ... first Great War gave very unsatisfactory ... Cats weighing 3 kilo could stand doses ... then tried in 10 human carriers but it pr... ported treatment of 11 carriers who had not been cured by injections of emetine. In all these cases the treatment was successful. He showed that an advantage is gained by administering emetine in the form of emetine bismuth iodide in chronic cases which have proved refractory to emetine. The effects of treatment are in some cases remarkable and all stages of *E histolytica* whether cystic or otherwise disappear from the stools. Emetine bismuth iodide was thought to be almost a specific against *E histolytica* and 2 or 3 courses were necessary to effect a complete cure. It should be noted also that if the first course fails to effect a cure a second course consisting of the same amount of drug administered for the same length of time is practically never efficacious. Both the dosage and the duration of treatment must be increased for the second course. Although undoubtedly failures after such courses have been reported the chances of curing carriers of *E histolytica* with this drug are greater than with emetine in the form of any other salt

On account of its being a very irritant drug a course of treatment with EBI ... very ... When

should be administered for three hours before the drug is given

Emetine bismuth iodide *is thought by some to be less efficacious in* acute dysentery than injections of emetine hydrochloride but Dobell and Low (1922) consider the compound to act equally well in acute cases in carriers and in all intermediate conditions. Lambert (1918) treated 40 Indian cases in Mesopotamia and came to the conclusion that in acute cases combined treatment *i e* emetine ... In relapsing cases ...ders that in emetine- ...cy in the treatment of amœbic dysentery preferably when the amœbæ are assuming their resistant stage. *He recommends it in 2 grain doses every night* for debilitated patients. Delayed vomiting indicates that the drug is beginning to take effect. Manson Bahr and Sayer (1927) state that many cases which fail to respond to emetine injections respond to emetine bismuth iodide. They are of opinion that the introduction of this drug has considerably raised the percentage of cures in chronic amœbic dysentery. They admit however *that such treatment is not ideal* from the patient's point of view and there is need for a less toxic and more efficient

drug The well known toxic effects which appear after administration of emetine bismuth iodide are also an objection to its use The degree of tolerance of patients to the drug varies considerably In the writer s experience in this country this drug has not proved satisfactory

EPI acts in the same way as emetine does but the consensus of opinion is that it is a more powerful amœbicide than emetine and its curative value is greater owing to possibility to re inforcement by iodine present in this compound

Treatment must be regulated by carefully watching the patient who should be kept strictly in bed In acute cases this is not difficult but patients who are carriers and have no definite symptoms may object If rest is rigidly enforced there is less sickness and there is less liability to heart trouble Emetine bismuth iodide generally produces diarrhœa about midway or a little later in the course this is often beneficial as it keeps the bowel thoroughly cleared in addition to the specific effects of the drug Towards the end of the course depression and general weakness are noticeable and in some cases the heart sounds may become very feeble and irregular The pulse should be felt daily and when this condition is detected the drug should be stopped When the course is over the patient quickly recovers diarrhœa ceases and the stools become solid

Diarr

It will be seen therefore that while emetine bismuth iodide is a useful drug in chronic cases it leaves a large residue of cases in which the infection is not eradicated even after several courses The treatment with emetine bismuth iodide is drastic but is said to cure 70 to 80 per cent of cases of chronic carriers When once a patient has resisted three courses of emetine bismuth iodide it is no use persisting with it Sometimes combination of the drug with yatren bowel wash (retention enema) or a vaccine made from bacteria infecting the ulcers may be successful It may also be said that the hope that the relative insolubility of the drug would prevent vomiting which is a very annoying tiresome and unpleasant complication in treatment has not altogether been fulfilled Emetine bismuth iodide is not so effective in the treatment of amœbic hepatitis nor can it be relied upon to prevent subsequent occurence of an amœbic abscess

Conclusion

(*b*) *Emetine periodide* (*E P I*) The dose is 2 grains (0 13 gm) thrice daily after food The course lasts for 15 days It is usually combined with 5 grains (0 3 gm) of exsiccated ox bile which is said to increase its action It contains 38 7 per cent of emetine and is insoluble in water It is not however well tolerated as was thought nor is it as effective in eradicating infection as EBI Emetine periodide aur emetine emetol and a number of other preparations of emetine have been prepared and tried with unsatisfactory results

Emetine bismuth iodide like emetine should never be administered unless the patient is strictly confined to bed The toxicity of this preparation is like that of emetine and its dose and duration of treatment should be carefully regulated It is often not possible to give the full dose of three grains daily to Indian patients and even doses of two grains daily are borne with difficulty The usual course prescribed is three grains daily for 12 consecutive days and any reduction in dosage and duration is followed by unsatisfactory results Often two or more courses have to be given and considerable strain is put on the heart The course may have to be stopped because of cardiac weakness When once started the course has to be continued for 12 days to be effective Nausea and vomiting are often troublesome The drug is given by the mouth in hard gelatine capsules, or keratin or salol coated tablets at night after meals with a cup of water or broth the patient lying flat on the bed. Nausea and salivat

Summary

on the first and second nights generally and there may be vomiting but after that toleration may be established Diarrhœa occurs after 4 to 6 days and if excessive, the dose may be reduced but the whole course must be completed After the course the patient is mentally depressed and weak The patient should be confined to bed for 3 or 4 days after the course is completed and for 2 to 3 weeks he should avoid all physical exertion The drug is not suitable for symptomless carriers or in abscess of the liver

Total alkaloids of ipecacuanha in amoebiasis Roux (1923) employed subcutaneous injections of the total alkaloids of ipecacuanha with good results In view of the fact that the amœbicidal action of emetine and cephæline is about equal, the use of the total alk
dysentery is worthy of trial
if the total alkaloids could be
line is more irritant and about twice as toxic and hence has never been widely employed

Other uses of ipecacuanha and emetine Ipecacuanha has been employed as an emetic and expectorant in the treatment ... oiratory organs. For this purpose it is of course pres ... cuanha increases the secretion of the bronchial mucos ... n may be of service by protecting the inflamed and ... brane from cold air and thereby lessening cough The effects probably are purely reflex. *It has also been* employed as a diaphoretic Emetine has been recommended for tuberculous hæmoptysis, ... istify its use for any internal *indicated* Emetine has also ... provement by destruction of ... a only occurs as a secondary

Emetine has been used in the treatment of a number of other diseases It has proved useful in the treatment of metazoan diseases particulary in various types of schistosomiasis.

Acton advised injections of emetine in one grain doses in the treatment of leucoderma. He believed that in addition to its action on *E histolytica* which is a common infection in *these patients the drug has a depressing action on the functions of the adrenals* which are hyperactive in leucoderma

Emetine in 1 grain doses has been given in sprue but it produces no beneficial effects.

Emetine has been tried in *oriental sore* Usually 20 minims of a 5 per cent *solution of* emetine hydrochloride in distilled water are injected at the base of the sore round its thickened margins Inflammation is set up and in 3 to 4 days the sore becomes a well defined ulcer *which is then treated on surgical lines* Emetine has no specific effect either in dermal or visceral leishmaniasis, the effect is purely a local irritant one

(3) *Mode of Action and Toxic Effects of Emetine*

The manner in which emetine acts in amœbiasis has lately been the subject of much ... in dilution of 1
by Dale a
in vitro,
in large

Dobell and Laidlaw (1926) devised a technique by which the *entamœbæ* could be grown on a liquid medium and t ... of the alkaloid was observed on the culture which ... With this technique *quinine concentration* ... *tolytica* as rich as the control Stovarsol ... ss *E. histolytica* was very susceptible to emetine in ... 000 of emetine hydrochloride or 1 in 1 000 000 of cephaline hydrocloride was lethal for *E histo-*

lytica in vitro within four days, provided the pH of the medium was about 7.0 With greater acidity of the medium the effect of emetine was much reduced These experiments demonstrate that the dose of emetine or other alkaloids required to kill *E histolytica* immediately bears no relation to the minimum dose of the same alkaloid which is eventually lethal if maintained for some time A very small quantity of emetine if constantly present in the intestines for days or weeks would probably suffice to make life therein impossible for *E histolytica*

It has been shown that changes in the cytoplasm of the amœbæ occur after an initial dose of one sixth grain and that after four grains the nucleus of the organism becomes disintegrated. The point worthy of notice is that in order to eradicate the infection one must aim at maintaining continuously over as long a period as is safe a sufficiently high concentration to kill the amœbæ

As regards the failure of emetine to kill entamœbæ in the cat it has been suggested that man and the cat may deal with emetine in different ways. In the cat most of the emetine is probably excreted in the urine and not in the gastro intestinal tract Some human beings infected with *E histolytica* appear not to react to emetine treatment This may not be due to emetine-resistant strains but possibly to the excretion of the alkaloid in larger quantities by the kidneys than by the gastro intestinal tract.

Emetine action in tissues

The other important factor lies in the tissues of the host and we have to find out if any change takes place in these so as to make it impossible for an obligatory tissue parasite such as *E histolytica* to penetrate the tissues and obtain the only food on which it can thrive and multiply It is said that entamœbæ do not touch emetinised red blood corpuscles Is it possible that the presence of emetine in the tissues of the host prevents this parasite from making use of them for its food? Or is it more likely that the presence of minute quantities of emetine prevents the entamœba by affecting its motility or some other function from penetrating into the tissues or using them as food, and thus it dies of starvation?

Be that as it may, there is no doubt that when we attempt to exterminate the protozoal parasites from the body, the administration of a drug like emetine destroys a large majority of these parasites The body resistance then ...ises and the patient's own power of resistance finally exterminate the residual ...parasites This undoubtedly occurs in kala azar and appears to hold good for ...malaria, trypanosomiasis and amœbiasis as well Two factors, therefore ...ppear to be concerned in recovery, (1) the natural resistance of the host and ...s tissues, and (2) the amœbicidal action of the drug A lowering of either ... these allows the disease to progress

Toxic Effects

In adult human subjects the figures for immediate massive toxicity are not ...own Fatal results however are to be feared with doses of 0 6 gm and anything ...ve a dose of 1.2 gm is probably fatal at once Eleven doses of 1 9 grains ...h would probably cause considerable damage in a man weighing 12 stone ...le 35 doses of 0 8 grain each would be fatal There should be long intervals ...ee months) between series of injections or courses, to allow the drug to ...xcreted from the body

No general disturbances or gastro intestinal symptoms are produced in man ... rule when a therapeutic dose is given by injection, local reaction as a ...s small when the solution is neutral Larger doses cause nausea vomit...nd diarrhœa As much as 0.25 gm has been given for a single dose without ...ing any other symptom except persistent nausea But if a very large ...f emetine is given the patient may suddenly faint and death may occur ...aralysis of the heart In more slowly developing cases there is persistent ... and vomiting diarrhœa, vertigo, extreme muscular weakness and ex...y dyspnœa, the pulse is at first slow and then rapid Death results ...xhaustion gastro-enteritis or intercurrent inflammation of the lungs. It ...be remembered that there may be wide differences in the toxicity of ... commercial samples of emetine

rare Cases of intolerance and hypersensitivity to emetine do occur, the symptoms produced being marked weakness, hyperaesthesia, diminished reflexes, vomiting slow pulse, abdominal pains and diarrhoea

Cumulative toxic effects of emetine Those who have had experience of treating amœbic dysentery are alive to the possibilities of the toxic action of this drug Low, in his series of cases, noticed diarrhœa secondarily arising during treatment with emetine and suggested that its unduly prolonged use in too high dosages might eventually produce symptoms of intoxication It is however very difficult to determine by clinical observation alone, whether the local effects on the *alimentary canal and the general effects of toxæmia* are to be attributed to emetine, or to the condition which had necessitated its administration

Dale and Dobell (1917) performed some very interesting experiments on healthy animals to elucidate this point They used chiefly rabbits and cats and employed doses which in proportion to the weight of the animals would be regarded as rather too high for continued administration in man The average weight of an adult man being taken as 65 kilo a dose of 1·0 mgm per kilo body weight is equal to about one grain for such a patient Cats weighing 3 kilo in these experiments were given doses of 5 mgm which works out to 1⅔ grains for an average man.

Such a dose given once only had no perceptible action of any kind on the animal and it could be repeated up to a point without any deleterious effects If, however the doses *varying from 3 10 mgm were continued for a fortnight sooner or later symptoms* of intoxication appeared and became rapidly intensified with persistence of the daily injections, leading to a fatal termination In rabbits a profuse diarrhœa attended with rapid emaciation was the prominent feature in cats these symptoms were of secondary importance and sometimes were altogether absent but lethargy and somnolence were marked and deepened to a terminal coma The toxic effects consisted of pronounced gastro-enteritis, acute nephritis œdema of the lungs weakness and paralysis of muscles Post mortem examination showed damage to the liver and kidneys in addition to signs of intestinal irritation, the heart was pale and flabby The results are very significant and clearly show the cumulative toxic effect of the drug in these animals They demonstrate the serious danger of pushing emetine beyond a certain point and ought to serve as a warning against the indiscriminate and unguarded use of the drug

Clinical experience has also established the fact that emetine is a cumulative poison in man The dosage and the length of time during which it *should be* given have therefore to be very carefully considered Formerly, untoward effects from its use were put down to the disease itself and this accounts for such diagnosis as post-dysenteric heart failure Recent investigations have shown that undoubted cases of sudden failure of the heart caused by emetine may occur The depressing effect of the drug, if given in doses of one grain daily for some time, is very marked, the noticeable features occurring after 4th to 6th injections being loss of appetite, nausea, vomiting, abdominal pain and diarrhœa due to gastro intestinal irritation

Minor toxic effects are weakness of the calf muscles, associated with numbness of the soles of the feet, a kind of woolly sensation or a feeling of stiffness in the popliteal space

Among the serious symptoms of poisoning are an increased pulse rate irregularity, listlessness and cardiac depression with fall of blood pressure. There may be general lassitude, disinclination to make an effort, weakness of the legs tremors of muscles, globus hystericus, cardiac arrhythmia, low blood pressure and a feeling of faintness General œdema, petechial hæmorrhages, purpuric skin rashes, desquamation of the skin, brittleness of nails hæmoptysis and signs of cerebral and pulmonary œdema may also be present Albuminuria sometimes occurs Polyneuritis is common and in some cases difficulty in swallowing and

a feeling of constriction about the throat and chest have been noticed Urticaria and large pruriginous plaques persisting for a month after the last injection have been known to occur even after a few injections Sudden collapse and death may supervene in some cases Auscultation of the heart in these cases shows similarity of sounds and a lack of the muscular element in the first sound C

the signs

noticed b

Chopra a

histological changes occur in the heart after emetine injections These consist of cloudy swelling disappearance of the transverse striations and atrophy and fibrosis of the muscle The writer (1934) has shown that degenerative changes are produced in the myocardium after therapeutic doses of emetine which can be detected by electro-cardiographic examination

Premonitory signs of poisoning

Th which a most careful daily examination i alimentary persisting nausea return of c azotemia slight albuminuria (iii) Circulatory grave hypotension, increased cardiac response to effort The appearance of any of this triad calls for immediate suspension of emetine

Emetine neuritis and myositis

Neuritis of the lower extremities is one of the early symptoms and is manifested at first by weakness in the legs difficulty in walking and interference with the normal reflexes Usually there is no pain on pressure as the motor nerve fibres only are affected Wrist drop ankle drop toe drop and hyperæsthesia of the soles of the feet sluggish knee jerks and loss of taste are noticed in some patients Sometime one particular group of muscles may be affected and the condition may resemble early progressive muscular atrophy The atrophy is preceded by myositis and muscular pains and probably a true myositis It is possible that difficulty in swallowing and the sensations about the throat and chest produced after emetine injections are due to involvement of the nerves supplying those parts, it has also been suggested that these effects may be due to changes in the nuclei in the medulla oblongata similar to those that have been observed in the cells of the anterior horn of the spinal cord In some individuals symptoms are produced after 8 or 9 grains of the alkaloid Palsy may develop some considerable time after the cessation of treatment Fibrotic changes in the nerve trunks have been noted after large doses of emetine in experimental animals and similar changes probably occur in man The effect of emetine however is more concentrated upon the muscle fibres rather than upon the nerve endings

Emetine has not been found in the cerebro-spinal fluid but it causes a slowly advancing paralysis of the central nervous system in frogs There is experimental as well as clinical evidence to show that peripheral neuritis is produced very early after a course of emetine injections Emetine does not affect the nerve fibres indiscriminately but has a predilection for those conducting motor impulses The weakness in the legs seen after emetine administration may also be due to damage of the muscle protoplasm

Emetine diarrhoea.

Emetine when given in considerable quantities produces diarrhœa It has already been pointed out that in animals emetine may produce gastro-enteritis with hæmorrhages in lymphatic glands spleen kidneys and thymus These experimental animals die even though emetine is discontinued directly the symptoms appear Diarrhœa which is the first sign of the gastrointestinal tract was quite common in the old days the rationale of ipecacuanha treatment being to push

the remedy till profuse diarrhœa was produced and the stools became liquid and of a canary yellow colour After discontinuing the drug the stool assumed its normal consistency, and to all intents and purposes the patient was considered cured Whether the cure was real or not is uncertain as in those days cysts were not recognised Low (1915) noticed that diarrhœa (occasionally with blood) occurred after hypodermic injections, but not so commonly as when ipecacuanha was given by the mouth It is not unusual for the patient to get a slight attack of diarrhœa after the sixth injection Since the oral administration of emetine bismuth iodide has come into vogue, diarrhœa has become more common, and when mild this is considered to have a beneficial effect and is not a sign of intoxication In addition to the specific action of the drug the bowel is at the same time thoroughly washed out and this mechanical process is valuable as is evident from the successful treatment of bacillary dysentery with saline purgatives A few days after the termination of the course (3 grains of double iodide for 12 successive days) the stools commence to become solid and in successful cases gradually assume normal consistency

Emetine is a protoplasmic poison acting equally on all tissues, heart failure being the actual cause of death In cases where the heart or kidney is affected it is advisable to give as small doses as possible for the treatment of dysentery In otherwise healthy individuals the number of injections should be limited as far as possible, and under no circumstances should more than one grain be given in 24 hours

Emetine, if administered continuously for therapeutic purposes depresses the heart but signs of cardiac depression improve when it is withdrawn Caution is indicated in all cases where the myocardium is damaged by other diseases such as malaria (malignant form), influenza, diphtheria, etc It is essential that the patient should remain in bed during the period of emetine treatment and an accurate record of the pulse rate should be kept If this is definitely increased, or palpitation occurs, the drug should be withheld till the heart resumes its normal rate

Convalescents who have received a course of emetine should be allowed to leave the bed very cautiously so that the effects of the drug pass off, and if the pulse rate goes up, they should return to bed The writer has seen patients *whose hearts were permanently strained for want of this precaution* Emetine is a powerful drug and appears to have a selective action on the heart muscle

It has been suggested that emetine should be avoided in pregnancy as it may cause abortion Some pharmacologists have stated that emetine increases the contractions of the uterus and have issued a warning against its use in pregnancy On the other hand clinicians have given injections of emetine in advanced cases of pregnancy without untoward results Recent investigations *have show* ... *whole of the* alkaloid is absorbe ... ot possibly be greater than 1 in ... effect on the isolated uterus an ... to relaxation Acton and Chopra (1923) showed that abortion is more common in cases of bacillary dysentery and is produced by the bacterial toxins, they showed that the toxin of *B dysenteriae Shiga* is a powerful ecbolic Emetine does not appear to be a causative factor in producing abortion and the coincidence of a miscarriage when injections are being given seems to be due *to the toxins of the parasite* rather than to the drug Pregnancy is not therefore a contraindication to the use of emetine In menstruating women it is preferable to start the injections after the period is over but in urgent cases treatment should not be deferred

5. Quinoline Derivatives

Since emetine is an isoquinoline derivative, other compounds of this group have also been tested for their amœbicidal action. More extensive investigations have been carried out with halogenated oxyquinolines and have resulted in the preparation of several compounds, yatren or chiniofon diodoquin vioform, etc which have been used in the treatment of amœbic dysentery The action of quinoline is reinforced by iodine According to Craig (1944) "among the iodine compounds which have been recommended for treatment of amœbiasis we possess the most efficient and safest therapeutic agents for elimination of this infection Many iodine compounds have been recommended for this purpose, but the most efficient are chiniofon, diodoquin and vioform"

(1) Chiniofonum

Composition

Yatren has been included in the B P under the name of CHINIOFONUM It is also called quinoxyl Chiniofon consists of a mixture of 7 iodo 8 hydroxy quinoline 5 sulphonic acid, 4 parts, and 1 part of sodium bicarbonate, it contains 26 to 28 per cent of iodine It is a light yellow odourless powder with a taste which is at first bitter and subsequently sweetish Experiments on amœbic cultures show that the drug has a specific effect on *E histolytica* the effective range being between pH of 5 6 and 7 8 in concentration of 1 in 5 000 It also possesses high bactericidal activity without deleterious effect on the tissues at the same time it acts as a cell stimulant

The drug was introduced in 1921 and was marketted under the name of Yatren 105, it is identical with Anayodin which is the name given to it by another manufacturer

Pharmacological action

Chiniofon is claimed to be a cell stimulant and a strong disinfectant. The action of yatren on cultures of *E histolytica in vitro* has been studied. A solution of 1 in 100 kills amœbæ in a few hours solutions of 1 in 1 000 inhibit multiplication in 12 hours and the cultures generally die out at the end of 24 hours with 1 in 1250 The amœbæ prove resistant to the action of 1 in 10,000 concentrations Taken by the mouth chiniofon is a gastro-intestinal irritant and produces diarrhœa in large doses Given intravenously in animals a 5 per cent solution produced no fall of blood pressure or other untoward effects Yatren is readily absorbed from the small intestine and from the rectum it is excreted in the urine which gives a positive oxyquinoline test *i e* green colour with ferric chloride Iodism is never produced though yatren contains 36 per cent of iodine

Toxic effects

Chiniofon is a non toxic drug and as a rule produces no marked toxic effects in the doses in which it is administered in the treatment of amoebic dysentery The only minor toxic effect produced is diarrhoea sometimes with a scalding sensation which usually persists for two or three days and is not usually excessive It is only in rare cases that it persists and the drug has to be stopped the diarrhœa then disappears In most cases decrease of dosage stops diarrhœa In Indian patients more than 3 0 gm of yatren per day generally produce diarrhœa, but no other toxic effects were observed

Toxic symptoms

Two cases of death after intravenous injections of chiniofon were reported by Maxon (1913) and pathological changes were found in the liver but the drug should not have been administered by this route

Toxic symptoms are rare but cases of acute or subacute fatty degeneration of heart liver and kidneys have been recorded after intravenous injections Compounds containing quinoline groups are said to be liable to produce necrosis of liver

Craig who has very large experience with this drug has never observed any toxic symptoms except diarrhœa

Chiniofon in Amoebic Dysentery

Chiniofon has now been tried in amœbic dysentery in a very large number of cases extending over many years and according to Craig (1944) it is a safe and efficient specific in the treatment of this condition Like all of the drugs

that have been advocated in the treatment of amœbasis it fails in certain infections but the records that are available and that cover over ten years of practical use of this remedy, show without question that it is curative in the majority of amœbic infections when properly administered and that serious toxic symptoms never occur

Although it can be given by the parenteral route it is given generally by the mouth or in form of enema

According to Craig (1944) Chiniofon is given in pills or tablets each containing 0.25 gm (4 gr) In adults three of these are given three times a day after meals for 10 to 11 days (100 tablets) This dose generally produces some diarrhœa and if it is too severe the dose may be reduced and then gradually increased to full dosage The diarrhœa unless severe is beneficial in eliminating amœba from the intestines The drug may be administered while the patient is doing his ordinary work and no particular precautions with regard to diet etc are necessary except that rich food should be avoided and alcoholic beverages are forbidden In children the dose should be given according to age and general condition

A course of 10 days treatment is usually successful in eliminating *E histolytica* in carriers and mild symptomless infections but if not the course should be repeated after ten days In patients with history of many diarrhœal attacks it will be necessary to repeat the course of treatment once or twice before the infection is eliminated as some of these patients show entamœba in their stools after the first course or have a parasitic relapse later

In acute and chronic amœbic dysentery emetine is first given till symptoms subside and stools become semiformed or formed not exceeding ten injections of one grain each, usually not more than 4 to 8 injections are required After this a ten days course of chiniofon as stated above is given

If chiniofon alone is used in acute amœbic dysentery the use of high enema with the drug is combined with oral administration in doses of 0.5 gm (7.5 gr) three times a day The daily enema is best given at night consisting of 200 ccm of a 2 per cent solution in warm water this should be retained for several hours if possible This treatment should be continued for 8 to 10 days, the patient remaining in bed

After convalescence is established the stools are repeatedly examined for the presence of amœba and if positive the treatment with chiniofon is repeated

According to Manson Bahr satisfactory and permanent results cannot be obtained when the drug is administered by the mouth alone In doses of two four grains (0.25 gm) pills three times a day it may produce considerable diarrhœa and fails to eradicate the infection It is much more efficacious when it is given per rectum Given in form of retention enemata the drug appears to be absorbed as is shown by its excretion in the urine in 24 hours the oxyquinoline test (green colour with perchloride of iron) is positive He describes the following technique of administration of retention enema

Technique of Retention Enema —The bowel should first be washed clear of mucus with a pint of 2 per cent sodium bicarbonate solution administered in the form of an enema After an hour's interval the patient lying on his left side with the buttocks raised on a pillow 200 cc of 2.5 per cent solution of chiniofon in warm water is run in slowly through a funnel and stout rectal tube The patient is encouraged to retain the

solution as long as possible changing on the dorsal decubitus and right side after every five minutes intervals thus allowing distribution of the solution on all sides of the large intestine The solution after retention for several hours is then passed out

The great danger associated with rectal medication that should be borne in mind is that the bowel wall may be friable. The mucosa is ulcerated and perforation may occur especially when high enemas are given with a rectal tube or catheter Even small enema (200 ccm) given under pressure may do this

Value of Chiniofon

[illegible] les 4 pillules (1.0 gm) [illegible] se proposed was 1 gm [illegible] he diarrhœa which was [illegible] d rest in bed If the sigmoidoscope showed the presence of ulcers a 2 per cent solution of yatren was employed for rectal lavage The ulcers healed up rapidly after contact with yatren solution Cure was recorded if six examinations of the stools on different days after cessation of treatment revealed no entamœba. No untoward symptoms were observed as a result of the treatment diarrhœa might come on after the second day but was rarely troublesome though it continued till treatment ceased Out of 50 cases who were given this treatment 28 were cured and others left before the requisite number of stools could be examined The percentage of cures both in cyst and trophozoite passers was 60.4 cure rate among cyst passers was proportionately higher The drug is therefore certainly worth trying in amœbiasis of the intestine whether acute or chronic and is of special value in patients with renal or hepatic conditions, and in cases of dermatitis in which carbarsone is inadvisable There is proof that yatren introduced per rectum percolates through the large intestines In a patient who had retention enemata of 2.5 per cent yatren and who died suddenly of coronary thrombosis autopsy showed yatren solution coating the mucosa of the large intestines After a ten days course of yatren by the mouth and per rectum relapses are frequent but the effects are good in those cases which have become resistent to emetine and EBI

In view of the above a combined treatment with EBI and chiniofon (yatren) per rectum has been recommended

It should be remembered that this form of treatment is troublesome to the patient and can only be carried out properly in nursing homes and in large hospitals Some clinicians have given the drug by intravenous injections but the results have not been superior to those by the other routes Yatren has also been advised in cases of amœbic hepatitis or even liver abscess, but it has no marked effect Patients suffering from bacillary dysentery derive benefit from it

Combined treatment

Combined EBI and Chiniofon treatment —Chiniofon is undoubtedly of value in the treatment of chronic cases of amœbic dysentery or carriers in combination with emetine injections or emetine-bismuth iodide by the mouth It has been abundantly demonstrated that both these drugs possess a definite curative value in amœbiasis which may be limited when they are used singly Chiniofon is readily absorbed but it is possible that it may not reach all the lesions in the bowels in sufficient concentration to kill the parasites Its action may be intensified when it is combined with emetine by injections The combination is well tolerated and gives very satisfactory results

The patient is put on light diet and a ten days course is given A retention enema is given at 8. 30 A M with the technique above described and retained till 5 OP M if possible Wher [illegible]

tablets the patient needs a few [illegible] course should be given but the strength of chiniofon should be increased in the enemata to 5 per cent and if necessary the combined course may be repeated again Manson Bahr considers this the most effective treatment of chronic

amœbiasis yet devised if it is conscientiously carried in all its detail Even w
this a small residue of uncured cases is left

(2) Diodoquin

osition

In diodoquin the sodium sulphonate radical of chiniofon has been repl
by a second iodine atom thus forming a double iodine compound with
formula 5 7 diodo 8 hydroxy quinoline The compound is tasteless very
soluble in water dilute acids and alkalies and only slightly in common org
solvents It contains 63 9 per cent of iodine (Chiniofon contains 26 to 28
cent Vioform 41 5 per cent) As the efficacy of these compounds is p
due to iodine it was thought it would be very effective Its insolubility h
ever acts against its effectiveness to some extent

Craig investigated this compound and found that the dose recommen
by the manufacturers was too small to produce any effect on amœbic infec
in dogs the dose was therefore increased and the drug was found to be
excellent and effective non toxic amœbicide

e

Diodoquin is supplied in tablets of 0 21 gm (3 2 gr) and its dose sh
vary with the severity of the infection In carriers and patients with i
symptoms 6 to 7 tablets are given in divided doses after meals and conti
for 20 days while in more severe cases 8 to 10 tablets are given The co
may be repeated after 7 to 10 days rest with the same or increased dosage
toxic effects or irritations of the bowel were produced Large doses such
three tablets three times a day for 20 days giving a total of 1 84 gm (28 8
were used with good results and no toxic symptoms The drug probably
prophylactic value also and Craig recommends two tablets after breakfast
two after dinner and considers these will suffice to kill any amœba inge

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as the usual course

In amœbic diarrhœa it is believed to be superior to chiniofon in dose
three tablets three times a day Excellent results have been obtained in a
amœbic dysentery

(3) Vioform and Enterovioform

Vioform is iodochloroxy quinoline and contains not less than 37 5 per
and not more than 41 5 per cent of iodine and not less than 11 5 per cent
not more than 12 2 per cent of chlorine It is a greyish yellow powder w
a faint aromatic odour almost insoluble in water and sparingly in alcohol
was used as a substitute for iodoform and was introduced in therapeutics in 1

ity

In therapeutic doses its toxicity is low and even with 100 mgm dose
kilo for 10 days rabbits showed no pathological injury In a single dose
250 mgm there was fatty degeneration in the liver with necrotic areas
some injury to the renal tubules

No toxic effects were noted in man with therapeutic doses except rar
headache palpitation dyspnœa colic or diarrhœa with mucus and blood

Dosage

In the treatment of amœbiasis it is given in doses of 0 25 gm (4 gr) tablets three times a day for ten days After an interval of one week another course of 10 days is given It is not as effective as chiniofon

The drug is given by the oral route in gelatine capsules On account of its irritant action it cannot be used per rectum In chronic cases and in severe infections larger doses may be used

Entero-vioform

The basis of enterovioform is vioform which is combined with saponin to emulsify it This compound is said to be useful in the treatment of carriers passing cysts Two tablets of the compound containing 0 25 gm are given three times a day after meals for a period of 10 days and the course may be repeated after one week No toxic symptoms have been observed

The writer has used this drug with good results, it certainly ameliorates symptoms

G Arsenical Compounds

A number of aromatic compounds of arsenic have been used in the treatment of amœbic dysentery of which Carbarsone is the best known

(1) Carbarsone

Composition and dosage

4 Carbaminophenyl arsonic acid or carbarsone is a white crystalline solid tasteless and odourless almost insoluble in water but soluble in alkaline solutions It contains 28 85 per cent of arsenic After oral administration it is absorbed and is excreted in urine It is the least toxic of the three arsenical compounds used in the treatment of amœbiasis

Clinical experience has shown that in therapeutic doses it produces no serious toxic effect but since it contains a substituted amino group in para position it must be used with great caution Toxic doses in animals produce lethargy diarrhœa and renal damage In man in a large series of cases when the drug was given in doses of 0 25 gm (4 gr) twice daily for 20 days it produced no toxic effects except slight gastric distress

Course of treatment

Th [illegible] days [illegible] the mo[illegible] the use of enemata along with the oral route gives no advantage The course of carbarsone should not be repeated before three months are over from the date of completion of the last course

There is as a rule no irritation of the stomach and the drug is retained without any difficulty

[illegible] successful enemas are advised This method of administration in writer's opinion does not eradicate infection

The action of the drug is due to toxic effect of arsenic on the amœba According to Craig carbarsone can be relied on to cure 85 to 95 per cent of the mild

amœbiasis yet devised if it is conscientiously carried in all its detail Even with this a small residue of uncured cases is left

(2) Diodoquin

In diodoquin the sodium sulphonate radical of chiniofon has been replaced by a second iodine atom thus forming a double iodine compound with the formula 5 7 diodo 8 hydroxy quinoline The compound is tasteless very in soluble in water dilute acids and alkalies and only slightly in common organic solvents It contains 63 9 per cent of iodine (Chiniofon contains 26 to 28 per cent Vioform 41 5 per cent) As the efficacy of these compounds is partly due to iodine it was thought it would be very effective Its insolubility however acts against its effectiveness to some extent

Craig investigated this compound and found that the dose recommended by the manufacturers was too small to produce any effect on amœbic infection in dogs the dose was therefore increased and the drug was found to be an excellent and effective non toxic amœbicide

Diodoquin is supplied in tablets of 0 21 gm (3 2 gr) and its dose should vary with the severity of the infection In carriers and patients with mild symptoms 6 to 7 tablets are given in divided doses after meals and continued for 20 days while in more severe cases 8 to 10 tablets are given The course may be repeated after 7 to 10 days rest with the same or increased dosage No toxic effects or irritations of the bowel were produced Large doses such as three tablets three times a day for 20 days giving a total of 1 84 gm (28 8 gr) were used with good results and no toxic symptoms The drug probably has prophylactic value also and Craig recommends two tablets after breakfast and two after dinner and considers these will suffice to kill any amœba ingested

The drug may be used in place of chiniofon in the treatment of symptomless carriers and mild infections and may be preferred in children as it produces no diarrhœa Two tablets three times a day for twenty days are recommended as the usual course

In amœbic diarrhœa it is believed to be superior to chiniofon in doses of three tablets three times a day Excellent results have been obtained in acute amœbic dysentery

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Vioform is iodochloroxy quinoline and contains not less than 37 5 per cent and not more than 41 5 per cent of iodine and not less than 11.5 per cent and not more than 12 2 per cent of chlorine It is a greyish yellow powder with a faint aromatic odour almost insoluble in water and sparingly in alcohol It was used as a substitute for iodoform and was introduced in therapeutics in 1932.

In therapeutic doses its toxicity is low and even with 100 mgm, dose per kilo for 10 days rabbits showed no pathological injury In a single dose of 250 mgm there was fatty degeneration in the liver with necrotic areas and some injury to the renal tubules

No toxic effects were noted in man with therapeutic doses except rarely headache palpitation dyspnœa colic or diarrhœa with mucus and blood in the stools

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Course of treatment

The usual course given by the writer is 0 25 gm (4 gr) twice daily for ten days In resistant cases a 15 to 20 days course is given The drug is given by the mouth in form of tablets or in gelatine capsules In the writer s experience the use of enemata along with the oral route gives no advantage The course *of carbarsone should not be repeated before three months are over from the date of completion of the last course*

There is as a rule no irritation of the stomach and the drug is retained without any difficulty

solut
tion
given in 3 grain doses (0 2 gm) to produce sleep so that the patient can retain the drug If enema is rejected it should be repeated and at least five successful enemas are advised This method of administration in writer s opinion does not eradicate infection

The action of the drug is due to toxic effect of arsenic on the amœba According to Craig carbarsone can be relied on to cure 85 to 95 per cent of the mild

infections He, however, believes that arsenical preparations should be used in those cases which do not respond to the quinoline and iodine compounds

The writer has found that the drug is much more effective if a small dose of a mild saline purgative, such as Siedlitz powder or fruit salt is given every morning while the drug is being taken Chopra and his co workers (1933) tried carbarsone in a number of cases of chronic amœbic dysentery with vegetative and cystic amœba in the stool, 0 25 gm of the drug was given twice daily for 10 to 20 days, the usual course being for 15 days A mild saline purgative was given daily whilst the drug was being administered, the criterion of the cure was six negative examinations during a fortnight following the treatment In a series of fifty three cases treated it was noted that the stools, as a rule became free from amœbæ three to four days after the beginning of treatment The proportion of probable cures to failures was 1 0 12, no toxic reactions were noted while the general toxic effect common to aresnicals was not very pronounced

A complete absence of toxic reactions has also been noted in patients given from 150 to 1,200 mgm per kilogram of body weight over a period of forty-eight weeks A number of mild reactions have, however, been reported in human beings, ranging from nausea vomiting diarrhœa, headache, sore throat *lachryma* ... and exfoliative ... nular ... ituted amino group in para position and must, therefore, be used with caution *It should* not be used in the presence of kidney or liver disease and is therefore contra indicated in amœbic hepatitis Certain cases of dysentery fail to react either to carbarsone or to any other amœbicidal drug

Ambiarson—Chopra, Sen and Sen (1935) reported on the use of a compound termed ... to that of carbarsone, ... a day for from ten ... nd a saline purge

Of forty patients who received this treatment twenty five were cured in ten the results were indeterminate and in five the treatment failed The ratio of probable cures to failures was therefore 5 7 1

... ohydroxyphenyl arsonic acid It contains ... e l this drug largely before the more ... dine were used This drug is definitely ... ter s opinion is in accord with this and

... no-para-oxyphenyl arsenic ... eported ... a rest ... so that

Indiscriminate use of the drug is not without risk but as this drug is rapidly excreted, it is preferred to stovarsol The toxic symptoms are chiefly erythema nausea and vomiting As in case of all arsenical drugs the drug should not be used in patients with disease of liver and kidneys Craig prefers treparsol to stovarsol but not to quinoline iodine compounds

Treparsol an arsenobenzene derivative has also been used in combination with emetine with good results

7. Holarrhena Antidysenterica

It is a small deciduous plant belonging to the natural order Apocyanaceæ It is also known by the name of *H codaga, H pubescens, H malaccensis, Wrightia*

antidysenterica, and *Chenomorpha antidysenterica*. Two species *H. congolensis* and *H. Wulfsbergii* growing in West Africa also have a reputation in the treatment of dysentery. In England it is known as bitter oleander, dysentery rosebay, oval-leafed rosebay or conessi bark tree. In Sanskrit it is called *Indrayav* or Indra's ... *Kurchi* and *Dubhi*, ... own as

... ous for ... the out ... the sub-Himalayan regions ... dian peninsula down to Malabar and Travancore and grows abundantly in the forests of Burma. *H. antidysenterica* is often mistaken for another species of the same family, viz., *Wrightia* ... in fact Linnæus was originally responsible for this confusion. In 1809 Brown ... In spite of this ... rt and it is ... ich attention, ... arrhena

Distribution

Both the bark and seeds of this plant are among the most important medicines of the Hindu materia medica, infusions made from these have been used in the treatment of dysentery for many centuries. The Hindu physicians consider the plant to have bitter, stimulant, antipyretic, astringent and antidysenteric properties. It is said to stop hæmorrhage, and is an expectorant and is used as a tonic. It forms part of many preparations in the Ayurvedic (Hindu) and Tibbi (Mohammedan) medicine.

Seeds. The seeds contain 29.36 per cent of a fixed oil and 0.025 per cent of the alkaloids ... from the

Chemistry

... udied first by Keidel (1878) who found ... us sensation and voluntary movements ... was depressed and the reflexes tended ... of the intestines and

(1923) on testing the tannins of kurchi bark and of ipecacuanha against the free-l[illegible] ciliate protozoon *Glaucoma* found both to be highly toxic to this organism The alka[illegible] have little or no effect on the bacilli of the dysentery group

The pharmacological action of conessine has been fully studied by Chopra and co-workers ([illegible]
in 2 800 c [illegible]
NaOH I [illegible]
in the pr [illegible]
histolytica was tested on the dysenteric stools of experimentally infected kittens. In mucus flakes in such stools it paralysed the motile amœbæ in dilutions of 1 in 280 000 in 8 minutes in the presence of an alkali and in 18 minutes in the absence of alkali Emetine in dilutions of 1 in 200 000 was found to be ineffective against the amœbæ but paralysed them in [illegible]

than emetine

Gastro intestinal tract These alkaloids have an inhibitory action on the activity of the digestive ferments such as ptyalin pepsin and trypsin The peristaltic movements of the intestines are inhibited The alkaloids have no emetic action and do not produce nausea.

Circulation Small doses 2 mgm injected intravenously into the saphenous vein of a cat weighing 2 kilo caused a persistent fall of blood pressure but without any alteration in the intensity or frequency of the heart beat Perfusion experiments with the isolated heart rarely showed any effect on the frequency or force of the contraction Doses of 1 to 5 mgm in a cat of 2 kilo showed no alteration in the auricular and ventricular contractions as seen in myocardiographic tracings

Uterus The total alkaloids have very little effect on the excised uterus or on the uterus *in situ*

Excretion The alkaloids are mainly excreted by the gastrointestinal tract and by the kidneys They can be detected in the urine soon after intramuscular or oral administration The excretion goes on for nearly a week after cessation of the treatment

Local effects of intramuscular or subcutaneous injection. When a 6 per cent solution was injected into the tissues no hæmorrhage or necrosis was observed but a good deal of œdema occurred at the site of injection The œdema was most marked in 24 hours and disappeared completely in 48 hours after the injection hyperæmia and œdema were due to the acidity of the salt of the alkaloids One to two grains of the total alkaloids give rise to no signs of hæmorrhage or necrosis such as is seen with emetine or quinine

The action of low melting point alkaloids has been worked out by Chopra and his co-workers (1933) and is very similar to conessine

There is no emetic or depressant effect in man when 20 grains of the bismuthous iodide salt of the total alkaloids are given daily for 10 days The pulse remains normal in frequency tension and rhythm There is no alteration in the heart sounds even in a case of cardiac disease The drug does not cause irritation of the alimentary canal in the way that emetine does If it does occur this is probably due to a co existing infection with *B dysenterica* (Flexner or Strong) The drug is however exceedingly bitter

In Amœbiasis

The bark and seeds of *H antidysenterica* have been used in the treatment of dysenteries of India for many centuries It appears to be used in the indigenous systems in two forms —

(1) As kurchi bark either in the form of a powder or watery extract

(2) As *Indra Jav* an emulsion of seeds Tull Walsh (1891) refers to the use of the bark as being approximately equal in its effects to emetine mercuric iodide The drug however was not tried properly in the treatment of dysentery until lately Tablets made

from the powdered bark have been put on the market by Burroughs Wellcome & Co, and have been combined with emetine injections This drug has been used as an adjuvant to emetine in the treatment of chronic amœbic dysentery with excellent results Different preparations of the drug have been tried in the treatment of amœbic dysentery

The drug is now used in one of the following forms —

(1) *Bark* Sixty grains of the bark in the form of tablets or 1 to 2 drachms of the extract are given orally every day for ten days The improvement is less rapid than with emetine but seem to be more lasting The ratio of probable cures to failures by this treatment in a series of 16 cases was 1 1

Emetine may be combined with *H antidysenterica* bark. The latter may be given either in the form of powder or extract together with a course of emetine injections In a series of 9 cases the ratio of probable cures to failures worked out to be 1 1

(2) *Conessine* One to two grains of conessine are given intramuscularly every day for 10 consecutive days The drug is well tolerated but the results are not so good as when the powdered bark or the extract is given Henry and Brown (1923) found the tannins of *H antidysenterica* bark highly toxic to free living protozoa and it is possible that the superior action of the powdered bark and the extract is probably due to the presence of these compounds The ratio of probable cures to failures in a series of 9 patients treated by this method was 1 2

alkaloids have also been given by the mouth they do not produce nausea or vomiting

3) prepared bismuthous iodide

Kurchi bismuthous-iodide

tract such as are observed in the case of emetine

The writer at first tried the effect of injections of the total alkaloids in 10 cases of amœbic dysentery some of which were acute and others chronic The drug was given in doses of one grain daily intramuscularly, a marked local reaction was however produced In this series there was one failure In another series of 20 cases kurchi-bismuthous iodide was given by mouth twice daily in doses of 4 grains curing 12 cases Two required a second course of these one was cured

rchi alkaloids is due the dysentery group ful when acting in a are three methods of l one that seems the

Modes of administration

ation That failures with

More recently Acton and Chopra (1933) by using the bismuthous iodide compound of the total alkaloids of Kurchi in doses of 10 grains (0 6 gm) twice

daily for 10 to 20 days, preceded half an hour before by a mixture containing one drachm of sodium bicarbonate and 40 grains (2 6 gm) of sodium citrate, obtained a proportion of probable cures to failures of 3 16 1 in a series of 78 cases This is now the standard method of treatment with kurchi alkaloid In obstinate and persistent cases, a prolonged course (1 to 3 months) of standardized extract of kurchi 1 to 2 drachms twice daily, with or without *plantago ovata* (Isabgul) is often effective The extract is extremely bitter to taste and many patients object to it

The third method is to give the drug in large doses in order to attain a sufficiently high concentration to be effective in an acid substrate Fortunately the total alkaloids of kurchi bark are not toxic, so that large doses can be given, and we can also form an insoluble bismuthous iodide compound which will not begin to act until it reaches the acid substrate in the cæcum and large intestine. This actually does occur, as qualitatively it is found that the kurchi alkaloids appear in the urine of patients taking the bismuthous iodide compound. *Entamoeba histolytica* may be living in the tissues or in the lumen of the gut. In the former case it will be in contact with the serum and body fluids at a pH of 7 2 whilst in the gut the contents may reach a high degree of acidity between a pH of 5 and 6.

The discordant results so far as kurchi bismuthous iodide is concerned are due to—

1 Some fault in the procedure of extraction of the alkaloids from the bark or preparation of the compound

2. The bark from which the alkaloids are extracted not being mature being improperly collected or being imperfectly dried

Kurchi bismuthous iodide was originally prepared in the *Calcutta School of Tropical Medicine* on the same lines as emetine bismuth iodide by the cold extraction process. Its approximate composition is as follows —Total alkaloids 27 per cent bismuth 22 85 per cent and iodine 50 15 per cent The dose is 10 gr twice daily preceded half an hour by an alkaline mixture In simple cases a course of 10 days duration is given when mixed infection exists 15 to 20 days may be necessary

Summary—Two preparations of Kurchi bark are used in the treatment of amœbic dysentery Kurchi bismuth iodide is given in doses of 0 25 gm (4 gr) *twice daily for ten consecutive days In relapsing cases and severe infections* double of this dose may be given for the same period without producing any deleterious effect The fluid extract of the bark is standardised to contain one half grain (0 032 gm) of the alkaloids in one drachm (4 ccm) of the extract. *The extract is given in doses of 1 to 2 drachms 2 or 3 times a day for a period* of 10 to 15 days in acute cases and for 4 to 6 weeks in chronic cases In relapsing dysentery the author has used the extract in doses of 1 to 2 drachms twice daily for months with courses of chiniofon or carbarsone in *between* with good results The disadvantage is that *the extract is extremely bitter* to taste.

8 Other Drugs in Amœbiasis

Compounds of mercury The antiseptic action of mercury compounds is well known and many of them have been tested *in vitro* in the hope of getting a compound which is more parasitotropic and less organotropic but none of them have been found effective in amœbic dysentery

Mercurochrome 220 has been tried in the treatment of amœbiasis For detailed description see the section on mercury

Kaolin also known as 'bolus alba' is a native hydrated aluminium silicate purified from sandy matter by elutriation Extensive deposits are found in China Deposits of kaolin are present in southern India It occurs as smooth white or yellowish white powder or in

lumps, insoluble in water, in cold dilute acids, and alkaline hydroxides It is a powerful adsorbent and has an earthy clay like taste and odour when moistened Internally it is used in doses of 3/4 to 1 ounce (8 to 30 gm) with water, milk or gum acacia emulsion

are adsorbed by animal charcoal but not by kaolin talc, kieselguhr or wood charcoal Tetanus toxin is adsorbed by all the above agents In general gram positive bacteria are adsorbed much more readily than the gram negative Colloidal kaolin has been tried intravenously in septicæmic conditions but it has a direct hæmolytic action on the blood, it also tends to produce allergic shock

On account of its adsorbing power kaolin has been given by the mouth in the treatment of acute bacillary and amœbic dysentery in doses of 20 to 30 gm stirred in water after a preliminary cleansing of the bowels with calomel It is particularly useful in cases where a large number of stools have been passed and symptoms of toxæmia are present It is undoubtedly useful in chronic cases Asiatic cholera has been treated by kaolin 400 to 800 gm being dissolved in a litre of water, three ounces or a wineglassful of this

to be entirely mechanical It is also t
dysentery, etc

emetine and bismuth

Kaylene is described as activated colloidal aluminium silicate It adsorbs toxins and is said to act as an intestinal antiseptic It has been recommended in chronic dysentery diarrhœa and also for Asiatic cholera

Bismuth Subnitrate—Deeks (1914) advocated large doses of bismuth salts by the mouth and as much as 180 grains of the subnitrate mechanically suspended in a glass of milk or water were given day and night every three hours Strict dietary was maintained during first ten days and afterwards a non-irritating diet was given Such large doses are not favoured in these days and toxic effects in form of cyanosis and forcible action of the heart occurred

Rivanol (2 ethoxy-6 9 diamino acridine lactate) is an acridine dye and is recommended to be given as an enema in 1 in 2 000 solution, 500 to 800 ccm being injected at body temperature the patient lying first on the left side and afterwards adopting knee elbow position Its action is said to be increased by administration of sodium sulphate by mouth A 1 in 1 000 solution kills *E histolytica* in culture in 20 to 24 hours Experiments on cats infected with *E histolytica* did not prove definitely its curative effect when given per rectum It produced spasmodic contractions of the smooth muscle of the gut very similar to those produced by papaverine Rivanol is given in tablets by the mouth in doses of 30 to 50 mgm daily Children recieve one tenth of the dose

Iodoform was recommended in doses of 50 mgm in keratinized capsules, first day one capsule second day two capsules, third day four capsules, fourth day six capsules and continued for 15 to 22 days, with indefinite results

Heptyl resorcinol Faust (1930) offered evidence that heptyl resorcinol is successful clinically in amœbiasis Of the many compounds only hexyl, heptyl and octyl resorcinol are available The toxicity of these compounds on oral administration appears to increase with the increase in size of the alkyl radicle Octyl resorcinol may be definitely ruled out because of its local irritating effects In natural *Balantidium coli* infestations in guinea-

p gs heptyl resorcinol was found to be definitely curative but in doses approaching the MLD hexyl resorcinol is less toxic than heptyl has a stronger antiseptic action and is worthy of trial

9. Summary of Treatment of Amœbiasis

Every person harboring *E histolytica* has a lesion either in the intestine or elsewhere There is no such thing as a healthy carrier Treatment should therefore be given in every case in which *E histolytica* is discovered and if possible the disease should be eradicated

It is most important that patients without symptoms or with mild symptom should be thoroughly examined both from therapeutic and prophylactic points of view For such cases the following treatment is advised —

Scheme of treatment for Entamoeba Histolytica carriers without co existing dysentery—

Days 1 10—Carbarsone 0 25 gram by mouth twice daily

20 25—Emetine hydrochloride 0 065 gram (one grain) daily intra muscularly

20 30—Carbarsone 0 5 gram by mouth twice daly

If stools positive on the 37th, 38th, or 39th day or on later clearance tests patient is to be treated on the lines as described under chronic Amœbic Dysentery

The following scheme of treatment is recommended in acute or subacute amœbic dysentery —

Days 1 6—Emetine hydrochloride one grain daily intramuscularly

1 10—Carbarsone 0 25 gram by mouth three times daily

10 24—*Diodoquin 0 63 gram by mouth three times daily* if stools negative on the 8th 9th and 10th days

If stools positive on the 10th day or symptoms persist

Days 10 20—Vioform 0 25 gram by mouth three times daily and chiniofon retention enemata 2½ per cent every other day 250 cc to be retained for eight hours

18 20—Emetine Hydrochloride 0 65 gm (1 grain) daily intramuscularly

NOTE —In the absence of adequate supply the following drugs in their respective dosages may be considered interchangeable —Chiniofon one gram three times a day vioform 0 25 gram three times a day diodoquin 0 63 gram

If the patient is seen during an acute exacerbation the same treatment as in case of an acute attack is given During the quiescent period the patient should be given a course of chiniofon diodoquin vioform or carbarsone (15 20 days) If after the course the stools still contain entamœba in vegetative or cystic forms the course should be repeated In case of carbarsone the course should not be repeated till three months after the previous course but during this period courses of chiniofon or allied compounds may be given

In very chronic cases who have repeated relapses the eradication of the disease is very difficult and treatment may have to be continued for months with suitable intervals Combined treatment with emetine bismuth iodide and chiniofon in form of high retention enemas has been recommended by some authorities

The treatment in these cases should be controlled with repeated stool and sigmoidoscopic examinations If either motile or cystic forms of entamœba, or ulceration, is present the course should be repeated

In these cases no one method of treatment is certain If one remedy fails, another should be employed The writer has tried courses of kurchi bismuth iodide combined with carbarsone or chiniofon with success In persisting cases repeated course of carbarsone or chiniofon or diodoquin and prolonged use of kurchi extract afterwards in doses of one to two drams (4 ccm) twice daily for a period of three months at a time, has produced useful results

The following plan of treatment is recommended in these cases —

Days 1- 6—Emetine hydrochloride gr I subcutaneous injection nightly
„ 5 14—Chiniofonum (Quinoxyl yatren) retention enemata 2½ per cent or 4 per cent each morning 250 cc to be retained for eight hrs
7 12—Emetine bismuth iodide grs ii or iii by mouth on an empty stomach each night
„ 13 25—Tabs amibiarson 0 25 gm twice daily after food
20 25—Emetine bismuth iodide grs ii or iii as before
, 29 31—Three stools to be examined for clearance
, 29 31—Sigmoidoscopy

A further examination of stool should be made during the period 46-53 day (i e 3 weeks after treatment) and if the bowel mucosa at the first sigmoidoscopy appeared unhealthy this examination should be repeated at this stage

Scheme of treatment for Amoebic Hepatitis and Liver Abscess —

Amoebic Hepatitis and Liver abscess

Days 1 9—Emetine hydrochloride 0 065 gram (one grain) daily intra muscularly
1 14—Chiniofon in doses of one gram by mouth three times daily
„ 13 15 } If clinical or laboratory evidence indicates advisability of further emetine therapy inject 0 065 gram (one grain)
, 30-35 } Emetine hydrochloride daily intramuscularly

Carbarsone is contraindicated in the presence of hepatitis

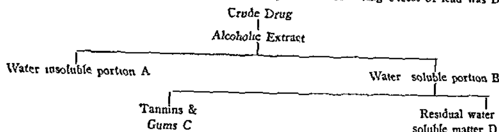
Supplementary therapy—Specific therapy should be supplemented with injections of liver extract administration of vitamins, especially B and C plasma, blood, or glucose transfusions when necessary

10. Palliative Remedies in Amœbiasis

As a considerable residuum of cases of amœbic dysentery is left uncured Henry and Brown (1924) examined a number of reputed remedies against this disease

The bark of *R adenodes* was [illegible]
other than tannins was found T[illegible]
methods with the hope of selec[illegible]
which seemed promising enough[illegible]
exhausted with boiling alcohol and the extract concentrated *in vacuo*, the thick syrup obtained was diluted with water to precipitate resinous and fatty matter and this gave

preparation A The liquor was further concentrated *in vacuo* to remove all alcohol and this was B This was treated with lead acetate to remove all tannins and this preparation was C and the residue after recovering the precipitate and removing excess of lead was D



The strength of this final product was adjusted so that 1 ccm represented a certain quantity of the drug All four portions were then tested on glaucoma an actively motile ciliate occurring in hay infusions A and D proved non toxic to this organism and B and C were toxic The activity was found to be due to one of the components of C and on testing it was found to be the tannin fraction.

It is interesting to note that the action of many of the drugs used against non specified dysenteries in India and elsewhere is due to their astringent effects and not to the toxic

(1) Plantago Ovata (Ispaghula)

This is known in the vernacular as *Ispaghula* or *Isabgul* It is a Persian herb which also grows in the Punjab, Sind and the United Provinces The seeds which are commonly used are imported from Persia into Bombay in large quantities In the Tibbi books the seeds are found described under the name of *Bazr i katuna* They are boat shaped and generally pinkish grey, but the colour may vary some being brown while others are nearly white with a pinkish tinge, the latter are preferred Isabgul is a well known and popular remedy in chronic dysentery in India. So commonly is it used in this condition even by Western practitioners that it has found its way into the B P C When steeped in water the seeds swell up giving out large quantities of a sticky bland mucilaginous substance with no tast- ... of the same genus exhibit similar properties, ... rnishes the brown variety of ... pecies of plantago are *P psylli* ... and *P lanceolata*

The pericarp which contains all the mucilaginous matter is removed from the seed and is sometimes prescribed instead of the whole seeds by indigenous practitioners It is sold in the bazar under the name of "Bhusi and it is administered in doses of 2 to 3 dessert spoonfuls 2 or 3 times a day When the seeds are roasted they are said to have a more astringent effect

The seeds were examined by Henry and Brown (1923) The chief constituent is the mucilage which is contained in the cells of the epidermis After excluding the mucilage they could find no active principles toxic to protozoa except tannins The author found a glucoside named *aucubin* in small quantities

The seeds on account of their emollient and demulcent effects, are commonly used in

Therapeutic uses

A number of proprietary preparations composed of the mucilage containing principle of the seeds have been recently put on the market

(2) Aegle Marmelos (Bael Fruit)

It is commonly known as 'bæl' tree and has many vernacular names *Billuaphal* or *Sriphal* in Sanskrit, *Bael* in Hindi and Bengali

The tree is indigenous and is cultivated all over India In Hindu medicine the root

Fruit

(1) *The unripe or half ripe fruit* This is regarded as an astringent, digestive and stomachic and is an excellent remedy in irritation of the alimentary canal owing to the presence of tannins or mucilaginous substances It is sometimes used in combination with opium by Ayurvedic practitioners

(2) *The ripe fruit* This is sweet and is considered as aromatic and laxative The dried pulp is pale yellow or flesh-coloured and when mixed with water yields a pleasant orange coloured 'sherbet' which has slightly laxative properties

marmelosin

The fruit is said to have an astringent action and this property is not lost by drying although fresh fruit is preferable It is said to possess a remarkable efficacy against dysentery and diarrhœa, so commonly was it used by Western practitioners in India in old

Therapeutic uses

days that it was included in the British Pharmacopœia in the middle of last century It was believed to be an invaluable remedy in obstinate cases of chronic diarrhœa and dysentery unatten[illegible]
is very [illegible]
recent [illegible]
tion of [illegible]
to proc [illegible]
disappe [illegible]
chronic dysentery is due to its demulcent properties and also to a certain extent to the tannins present in it The drug is worthy of trial in chronic *amœbiasis where other remedies have failed*

Preparations

(1) *Extract of bael* This is made from fresh unripe fruit Dose ½ to 1 drachm 2 to 3 times a day

(2) *Liquid extract of bael* This is prepared from dried slices of unripe fruit Dose ½ to 1 drachm several times a day It is said to be much less effective than the fresh extract

(3) *The powdered dried pulp* This is said to keep well in airtight bottles Dose ½ to 2 drachms in chronic dysentery

Decoction of the dried bael fruit and syrup made with fresh or dried fruit are also used

(3) Acorus Calamus

It is commonly known as 'sweet flag' in English, 'Bach' in Hindi and Bengali It is a semi aquatic perennial herb with an indefinitely branched rhizome It is really a native of Europe and North America but is cultivated in damp marshy places in India at an altitude of 3000 to 6000 feet, it has established itself on the edges of lakes and streams The long creeping horizontal rhizome is collected in the autumn, cut into pieces and dried [illegible]

dysentery with good results [illegible]
is due to the presence of tannins

(4) Helicteres Isora

It is commonly known as the East Indian screw tree belonging to the Sterculiaceæ family In Hindi it is known as *Marar* or *Mararphali* (or the pod used in dysentery) in Guzrati it is known as *Mriga shingha* or deer's horn *It is a tall shrub or a small tree* resembling the common hazel It has bright red and showy flowers which appear in the rainy season The plant grows in Western India *and in Kashmir According to* Ainslie it is used by Hindu physicians as a remedy for offensive sores inside the ear It also forms part of prescriptions used *for* the cure of griping in the bowels and flatulence especially in children The pods have demulcent and slightly astringent properties

The writer analysed the pods *but no active principles* with the exception of tannins and the demulcent substances could be discovered

The pods are used in some parts of India in *the treatment* of chronic dysentery In some patients the symptoms are considerably ameliorated

(5) Castela Nicholsoni

The 'chaparo' (any part of the plant root leaves bark) is powdered and measured

per and enemata at 10 a m and
The decoction has a very bitter
pear to have been benefited by
chaparo

(6) Simaruba Bark

Simaruba bark is obtained from various species of Simaruba *S officinalis* *S amara* *S glauca* etc It was brought to Paris in 1713 from Guiana, where it was said to have been used with success by the natives in the treatment of dysentery It soon gained a reputation in Europe and was imported in large quantities The active principle of the glucosidal properties manner as chaparo me way It does not eldom employed

Uzara

Uzara is another African plant belonging to the N O *Asclepiadaceae* It is a proprietary article recommended by certain German workers but is of doubtful efficacy It is given in form of a tablet The alcoholic extract is known as *Panzaron*

Ya Tan Tzu

Ya Tan Tzu is the chinese name for the seed of *Brucea* Sp called by some *Brucea Sumatrana* by others *B javanica* and *B amarissima* It has been found to contain an alkaloid 'brucamarine' and a bitter glucoside 'Kosamine" the seeds contain also a small quantity of hydrolytic enzyme 1 8 per cent of tannin 20 per cent of a fatty oil and two bitter principles.

Two per cent cold infusion of powdered seed freed from the oil killed amœba instantly in vitro The ethereal extract has also an amœbicidal action but the expressed oil has not For the treatment of dysentery acute and chronic it is given in doses of 20-50 seeds (shells removed) If amœbæ are still seen after 2 or 3 days the dose is increased The treatment appears to be effective The amœbæ disappeared from the stools in an average of 2 6 days The drug is easy to administer only a few doses are needed and it is cheap

DIARRHOEAS OF PROTOZOAL ORIGIN

11. Balantidiasis

Balantidiasis is also known as Balantidial dysentery or Ciliate dysentery

It has been shown that forms of diarrhœa or dysentery caused by a ciliate protozoan *Balantidium coli* may be met with in man This ciliate is common in pigs and monkeys and may produce in them a fatal form of dysentery Human cases have occured in those who are intimately associated with pigs by faecal contamination of food and hands Cases have been recorded in many of the countries all over the world and fatalities have occured The parasite penetrates into the intestinal wall in the same way as *E histolytica* and is found in the blood vessels of the mucosa and submucosa There is at first hyperaemia of the wall, punctiform hæmorrhages follicular swelling and overproduction of mucus, the ulcers formed have irregular undermined edges The parasite penetrates the wall and invades the gland ducts, dissolving the muscularis mucosae by cytolysis The cysts of this parasite are infective and are viable in the faeces for weeks in moist and shade, they are rapidly killed by drying and sunlight

stimuli transmitted through the sympathetic
vasomotor

which definitely causes ingesting red blood cells In the connective tissue *Trichomonas* to be secondary invaders and say that the bowel damaged by dysenteric toxin take considerable time to recover and a heavy infection with flagellates probably act as irritating agents they should, therefore be eliminated

There is no specific treatment, though the organisms disappear after vigorous lavage with a 2 per cent sodium bicarbonate solution Stovarsol in 4 gr doses for 8 to 10 days is said to exert a specific action on *Trichomonas intestinalis*

Trichomonas vaginalis is easily implanted on a negative virgin vagina from the urethra of the male Attacks of typical dysentery are said to be caused by heavy giardia infection of the colon and such symptoms are more common in children When the small intestines are affected there is great tendency to chronicity and periodicity of symptoms and presence of giardia in the stools When giardia disappear from the stools cysts appear It has been said that this infection may produce any combination of abdominal symptoms leading even to a surgical operation, the suspicion of tuberculosis has also occured Giardiasis may occur in association with steotorrhoea microcytic anæmia and achlorhydria suggestive of sprue or para sprue

Excellent results have been reported from vaginal insufflation with sulphathiazole or sulphadiazine powder in the treatment of Trichomonas infection A powder containing sulphathiazole 1 part and betalactose 3 parts was used Eight gm of the mixture was insufflated daily for four treatments Flagellates lost their motility in ten to fifteen hours Blood sulphathiazole levels were not raised to dangerous levels, which is quite understandable, as 2 gm of the drug daily would not be a large dose

14. Intestinal Coccidiosis

Three spec

man *Eimeria clupearum* and sardines and which is parasitic in man and typical cysts The fæces len crystals There is a us or blood The oocyst gns and symptoms which flatulence and loss of weight

Isospora hominis also known as *I belli* is probably a parasite of epithelial cells of the small intestine The oocysts vary in length from 25 to 33 u and one half as broad, when passed fresh they are transparent and colourless in human fæces The infection is world wide and it is probable that in man it completes its schizogenic development in the mucous membrane of the intestinal villi The symptoms produced are those of sub-acute dysentery and the fæces are light coloured and contain large quantities of undigested matter and excess of fat

This consists of giving bismuth salicylate and charcoal three times daily

The disease is of short duration and limiting in character and often no treatment is necessary

CHAPTER II

TRYPANOSOMIASIS

AFRICAN TRYPANOSOMIASIS—CHEMOTHERAPY OF TRYPANOSOMIASIS ANTRYPOL (BAYER 205 GERMANIN), OTHER DRUGS DIAMIDINO STILBENE ANTIMONY COMPOUNDS ARSENICALS—SUMMARY —SOUTH AMERICAN TRYPANOSOMIASIS

Trypanosomes infecting animals

Important trypanosoma infecting animals are —*T brucei* causes fatal disease in horses and cattle *T evansi* produces disease in horses in India called 'surra' and is believed to be transmitted by the biting of flies *stomoxys* *T equinum* causes fatal disease in horses in South America *T equiperdum* and *T evansi* infect horses in many parts of the world *T congolense* (*T dimorphon*) causes disease of cattle, sheep, goats, pigs and dogs in Africa and game may serve as reservoir *T vivax* is an active species occurring in cattle, sheep and goat *T lewisi* occurs in rats

1. African Trypanosomiasis

The African trypanosomiasis is also called sleeping sickness or Negro lethargy

Vector and distribution

It is a protozoon infection caused by a flagellate named *T gambiense* (*Var T rhodesiense*
G palpalis,
Diptera *e.g*
lethargy
adenitis r
encephalitis
sense infection
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million cases are treated every year

T gambiense Var rhodesiense and T cruzi infect man the latter causing American trypanosomiasis *T gambiense* occurs in the blood lymphatic system and cerebrospinal fluid of man and domestic animals The infection is transmitted by tsetse flies but human trypansomes may also be transmitted by coitus and disease in horses known as dourine is transmitted in this way

Recent evidence has shown that human beings are the most important source of infection for the vector In other regions wild game may serve as a reservoir of infection particularly some species of antelope *e g* bush buck water buck, etc domestic animals also act as reservoir (nagana due to *T brucei*) Instances of human beings infected with trypanosomiasis and apparently in good health have been reported and such persons may act as reservoir

After ingestion of blood by the fly the parasites multiply in the mid and posterior

The fly after imbibing blood containing trypanosomes becomes infective in 18 to 34 days in rare cases in 53 days It then remains infective for 188 days, *i e* for the rest of its life Direct mechanical transmission by blood on the proboscis of glossina also occurs and may be responsible for some epidemics

Pathology

The tissues chiefly affected are the lymphatic glands and the central nervous system There is proliferation of lymphocytes and reticulo endothelium The fever in early stages is followed by meningo-encephalitis and meningo myelitis The vessels of the brain and cord are compressed resulting in malnutrition, cerebral changes and the desire to sleep The trypanosomes are distributed in the brain in an irregular manner There is adenitis of the neck groin and other glands The cerebro-spinal fluid is turbid and the dura mater

thickened and adherent, the spinal cord shows congestion and hæmorrhage There may be ascites and the pericardial fluid is increased, the spleen is often enlarged

The cerebro spinal fluid in early cases may be normal, it shows trypanosomes after about 3 months (on centrifugalising) and always after one year after infection. There is increased pressure and proteins are present, cell count may go to 1 000 per ccm (lymphocytes mononuclears, eosinophils), in unfavourable cases the mulberry or muriform cells are present Blood shows definite anæmia and decrease of hæmoglobin

Two stages of the disease have been described febrile or glandular and cerebral

Stage I —Incubation period may be 7 to 21 days from the time of bite to appearance ... re is characteristic local reaction at the site of the bite ... uncle about an inch in circumference appears surrounded ... After 14 to 21 days or longer rigor and fever appear, ... temperature approaches normal in morning and 103°

Erythematous eruption consisting of pinkish patches irregular in position and outline round or oval in shape with a clear centre appear on the trunk and thighs The skin is dry and pruritis is often present Glands enlarge in the posterior triangle of the neck at first soft and elastic later hard and fibrous, on puncture they show trypanosomes Karendels sign i e slightest pressure feels like a bruise and is very painful, a puncture with a needle feels like a hot poker and an accidental knock gives excruciating pain There is asthenia anæmia weakness wasting conjunctivitis and keratitis Low irregular pyrexia may go on for months with temperature of 99° to 100°F in the evening or may end spontaneously or after treatment

Cases are clinically divided into 3 groups —

Cases are clinically divided into 3 groups —(1) those in good health with trypanosomes in blood and with some fever, they are dangerous fertile source of infection to others (2) those (75 per cent) showing definite clinical symptoms who have a tendency to go to sleep in the day time they have enlarged lymphatic glands which on puncture show trypanosomes (3) advanced cases (13 per cent) which show high mortality Their speech and mentality is affected and they are in a *stupurous condition*

... 4 to 8 months

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reflexes are increased at first then lost, speech is slow ... and tired person, Rombergs sign may be present, later rigidity of neck and legs appears pulse rate is 90 to 140 per minute, and out of proportion to temperature

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pneumonia,

... blood (thick f ... is conc ... od and ... on of ... present Animal inoculation (rat or monkey) and blood culture on NNN medium are helpful

The disease should be differentiated from malaria syphilis *kala azar and in later* stages from cerebral tumour and encephalitis lethargica

... treatment of the infected control of people coming ... moval of population from highly infected

from ... ices and *destruction of* animal reservoirs

area ... clearing of bush etc

Fle

Chemoprophylaxis by intravenous injections of Bayer 205 (antrypol) was considered to be effective but later experience has shown that these do not always prevent infection It was found in Congo that intravenous *injections of 1.0 gm* in case of adults and 0 3 to

07 gm in case of children gave protection for some months In other cases protection lasted for three months at least Even if infection is not prevented the pathogenicity of trypanosomes is mitigated

Prognosis

Untreated cases are invariably fatal If adequate treatment is given in the early stages of the disease, the prognosis is good It is now established that the disease is curable Inadequate treatment with arsenical and antimonial drugs may give rise to resistant strains of trypanosomes

Treatment

The earlier the disease is recognised and the treatment is started the better the chances of cure The treatment with drugs should be regularly and adequately carried out and complications such as malnutrition etc, should be promptly dealt with The two effective drugs are Bayer 205 and Tryparsamide

2. Chemotherapy of Trypnosomiasis

(1) Antrypol (Bayer 205, Germanin)

(1) *ANTRYPOL* (*Germanin Bayer* 205 *NAPHURIDE*)

General

This is a complex organic combination (the symmetrical urea of sodium m amino benzol m amino p methyl benzol 1 napthylamino 4 6-8 trisulphonate When used in veterinary

Germanin is a fine white flocculent powder which dissolves easily in physiological saline and cold water The solution is faintly pink, odourless slightly bitter in taste and neutral to litmus The drug can be sterilised by heating in a water bath for 15 minutes but solution in sterile water renders this unnecessary Solutions can keep for some length of time but it is advisable to give freshly prepared solutions The drug both in a pure state and in solution should be kept away from light in amber coloured bottles A 10 per cent solution is injected intravenously in man and it is also said to be well borne sub cutaneously intramuscularly and orally The intravenous route is preferable

Pharmacology

Little is known about the pharmacology of this drug It is slowly absorbed from the alimentary tract In animals the drug has been found remarkably non poisonous The *dosis tolerata* has been estimated to be 160 times that of the *dosis therapeutica*. It could be given intrathecally to a dog in doses of 07 gm without producing irritation or other ill effects The drug is said to circulate in the blood for some time without losing its efficacy It probably combines with the proteins of the serum and in this way is fixed and retained Its presence can be detected in the internal organs for as long as 5 months after treatment As the drug circulates in the body for weeks or months it is not recessary to repeat it too often The trypanosomes develop a certain amount of resistance to it and it has toxic effects on the host Its action on trypanosomes is said to be inhibitory to the multiplication of the parasites The drug produces disappearance of the trypanosomes from the peripheral blood and in this way transmission of infection to the flies is prevented and the spread of disease is checked

Mode of action

The mode of action of Bayer 205 is not properly understood The drug produces no

increased power of resistance is not attributed to the protective power of the drug alone as the same phenomenon was observed in infected animals treated with Bayer 205 It is suggested that the drug combines in some way with the trypanosome cell producing a heterogenic antigen capable of stimulating the formation of specific antibodies The action of the drug is not therefore purely parasiticidal Along with this property there may be

an immunizing activity which completes the cure and affords an increased resistance in subsequent infections

Duncan and Manson Bahr (1923) found that in mice the drug in the kidneys produced extensive degeneration and exfoliation of the epithelium of the convoluted and other secreting tubules of the cortex The straight tubules and excretory ducts appeared unaffected Some of the tubules contained hyaline casts and there were necrotic foci The blood vessels were engorged minute hæmorrhages occurred in the cortex and vessels showed perivascular round cell infiltration The liver and the lungs were engorged and fatty changes and focal necrosis occurred in the former Minute hæmorrhages also occurred in the lungs and in the brain Marked anæmia was produced In experiments in which the object is to produce sterilisation after a single dose a great leucocytic reaction may be observed in relation to the sudden disappearance of parasites and death may result from shock The drug circulates in the blood for days and even months and consequently repeated doses have a cumulative effect Regular examination of the urine is necessary and the appearance of a considerable amount of albumin is an indication for stopping the treatment

Germanin has had a thorough trial extending over many years and its great value in early cases of the disease when the central nervous system is still uninvolved is firmly established The utility of the drug varies with the type species of [illegible] nmencement of [illegible] tive but in its late [illegible] anin has to be followed with tryparsamide In the case of rhodesiense infections also germanin is effective in early stages but the treatment has to be continued with tryparsamide when the nervous system is involved

It is generally given intravenously but it can be given intramuscularly The intrathecal injection causes pain vomiting headache convulsions and itchings even after small doses and cannot be recommended Besides advanced cases are not benefitted by intrathecal injections

The drug appears to be well tolerated and produces less toxic effects even in large doses in animals infected with trypanosomiasis than in normal animals

The average dose by the intravenous route is 1 0 gm dissolved in 10 ccm of distilled water, the total amount necessary to effect a cure being 10 0 gm The trypanosomes however disappear from the peripheral blood even after an injection of 0 5 gm but reappear This is the case with some of the other drugs and the doses have therefore to be repeated at weekly intervals

Different workers have adopted different courses Bayer 205 is given in doses of 1 0 gm on the 1st 3rd 10th and 13th days with good results In severe cases individual doses of 1 5 to 2 0 gm have been given in adults In Nigeria 1 0 gm doses of Bayer 205 followed by five 2 0 gm doses of tryparsamide was adapted

Some individuals have an idiosyncracy to the drug and collapse and death may result It is therefore advisable to give a trial injection of 0 3 gm of Bayer 205 before a full dose is given If an individual shows toxic effects the drug is withheld

Experience has shown that 0 102 gm of the drug per kilo body weight is usually well borne The drug however has been shown to have a cumulative action and circulates in the blood for a long time several months after a course of injections

The drug is irritant to the kidneys and may produce nephritis albuminuria

may occur after 3 to 4 injections but this may be temporary and may pass off In some cases the cerebro spinal fluid improves several months after the treatment is stopped and the condition may remain stationary In the majority of cases the disease progresses to a fatal termination In those cases in which the cerebrospinal fluid is normal and the infection is confined to glands and blood stream the drug is efficacious The earlier the treatment is started the better

Dosage and method of administration

In human beings it is advisable to start with 0 5 gm intravenously and if it is well borne to give 1 0 to 1 5 gm after 24 to 48 hours The dose can be

between injections allow the trypanosomes to become resistant

The trypanosomes do not disappear from the blood so rapidly as under tartar emetic atoxyl etc As a rule the blood is not free from the parasites till the second or third day after the injection Frequent examinations of thick blood films or centrifugalisation of blood in citrated saline are necessary in cases of relapse to demonstrate the presence of the parasites Sometimes isolated parasites appear after a few weeks but these disappear without further treatment The best test for cure is to inject the infected blood into small experimental animals and see if the disease can be transmitted. Clinically the action of the drug is apparent by disappearance of the glandular swellings in the neck diminution in the size of the spleen improvement of the blood picture increase of body weight and general mental well being

Toxic effects

Although toxic reactions are remarkably few in number the drug should be carefully administered Vomiting may occur if it is injected too rapidly Renal epithelium may be damaged and this is by far the commonest toxic effect of the drug Albumin in the urine generally occurs after the third or 4th injection there may be blood and casts and fatal anuria may occur Symptoms of urinary irritation may subside after the termination of the course of treatment but occasionally they persist When patients are undergoing treatment a careful watch should be kept on the blood and the urine The presence of albumin in the urine gives a warning although many authorities do not consider it a contra ind cation to the use of the drug care however is indicated in such cases Album nuria may sometimes occur even after small doses In many cases it disappears after a few doses without leaving any permanent after effects Some authorities do not hold albuminuria to be necessarily an indication for the interruption of the treatment in patients whose kidneys are at other times normal An erythematous rash sometimes appears commencing on the forearms and spreading to the rest of the body The eruption consists of central raised papules rather patchy in d stribution and finally it disappears by desquamation Pruritus is a constant accompaniment and purulent conjunctivitis and stomatitis may occur Cases [illegible]
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Experiments conducted in Africa show that Bayer 205 and Fourneau 309 have a definite prophylactic value A dose of 2 gm of germanin given to an adult is said to protect against any of the two *trypanosomes for* a minimum period of three months Within certain limits, administration of two or three *small doses at intervals* of a few weeks each, offers better protection than the administration of *one big single dose Protection* against rhodesiense infection is relatively greater than gambiense infection Other workers consider that protec *tion is not* of more than six months duration Administration of the drug in doses of 1 0 gm every two or three months is recommended in those entering *highly* endemic areas

The efficacy of chemoprophylaxis may be due to the fact that though rapidly excreted or destroyed, *the chemical compound may lead to a long persisting* elevation of the defensive powers of the tissues In the case of trypanosomiasis there is no evidence in support of this mode of action The compound may be excreted or destroyed so slowly that it continues to circulate and exert a trypano cidal activity for a long period or finally it may form a relatively insoluble local *deposit in the tissues from which small amounts continually pass into the body* fluids to act on the parasites

In order to be of value as a chemoprophylactic against sleeping sickness for any length of time a drug, it appears, must maintain a trypanocidal titre in the serum Since the trivalent arsenicals and arsphenamines produce a high trypanocidal titre in the serum for only a comparatively short period, they should *on theoretical grounds,* be of little value *in* prophylaxis, and this, in fact, has been shown to be true experimentally Quinquevalent arsenicals on the other hand are present in the serum in a trypanocidal titre for a much longer period,
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venously The period of [illegible] months and
the number of fresh infections among those prophylactically treated was twelve times less than among the untreated controls Even so, the results were not as successful as with germanin The prophylactic action of germanin is due *to the fact that concentrations in the* blood of 10 mgm per 100 ccm and not infrequently as low as 1 gm per 100 ccm are sufficient to inhibit the power of trypanosomes to infect the mouse It has been shown that concentrations of 1 mgm of germanin per 100 ccm can usually be detected in the blood five to six months after intravenous injection of a rabbit with 100 mgm per kilogram of body *weight The amount of germanin in the blood* is usually greater when a number of small doses of germanin are given over a period of a few weeks than when the same amount of the drug is given in a single injection (Findlev Chemotherapy, 1939)

(2) Other Drugs in Trypanosomiasis

(a) Diamidino Stilbene

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tried out on such cases The results are not very encouraging and do not justify hope that the drug will prove as efficacious as antrypol and tryparsamide even if in large doses over a long period

(b) Antimony Compounds

Antimonyl tartrates have a remarkable effect in diseases produced b trypanosomes in animals It was found that 1 mgm of antimony caused immediat disappearance of the parasites in rats weighing 200 gm. Plimmer and Thomson (1908) noticed the sterilising effects of potassium and sodium antimonyl tartrates in laboratory animals infected with *T brucei*, and *T evansi* Rats inoculated with nagana died in an average time of 5 to 6 days If on the fourth day, when the blood was full of parasites, 5 mgm of tartar emetic were injected subcutaneously, the parasites, were killed and the rats usually survived and some recovered completely, relapses, however, not infrequently occurred Arsenic and some aniline dyes produce the same type of effect, but are inferior to antimony compounds in this respect A large number of other antimony compounds were also tried in the treatment of this infection in animals and rapid disappearance of the parasites after intravenous injections was observed The effects were so rapid, that there appears to be little doubt that the trypanocidal action is due to antimony, and not to the formation of antibodies No evidence of agglutination or phagocytosis has been found

The immediate trypanocidal action of the trivalent antimony preparations *in vivo* (also highly effective *in vitro*) as compared with the delayed action of the pentavalent preparations, revealed an essential difference in the action of these two groups In the same way as with arsenical compounds, a reduction of the pentavalent preparations to the trivalent form is assumed to take place within the system

Antimony compounds were first tried in the treatment of human trypanosomiasis many years ago Borden (1910) treated sleeping sickness in the Congo with injections of tartar emetic Kerandel treated himself with injections of tartar emetic after failing with atoxyl Owing to the chronicity of the disease, and the great tendency to relapse after long intervals of absence of the parasites from the peripheral circulation it is very difficult to draw any conclusion regarding the curative effects of the drug The successful treatment of trypanosomiasis entails strict control over the patient, possibly for two years The treatment of sleeping sickness with antimony has receded into the background as compared with Bayer 205 (Germanin)

In the treatment of animal trypanosomiasis antimony is also used in the form of antimosan veterinary In Nagana an important trypanosomal disease of cattle, antimosan is effective both as a curative and prophylactic drug It may be used alone or in combination with Bayer 205 (Germanin)

(c) Arsenicals

Arsenicals

Tryparsamide is a valuable drug in the treatment of advanced cases Orsanine is a French equivalent The drug is a colourless crystalline solid, freely soluble in water forming neutral solution It may be given intramuscularly or intravenously, the latter method being preferred The average dose is 0 045 gm o 0 05 gm per kilo body weight and even with this dose ocular symptoms may evelop It is recommended by some authorities that the starting dose should 0 04 gm per kilo body weight Children stand the drug well

adult dose being tolerated The drug to be *effective* should be pushed to limit of safety and 15 weekly injections of 0 045 gm per kilo is the usual course though some only give 12 injections

A second course should be given after 1 to 3 months have elapsed after the first course

Tryparsamide is less effective if previous injections of *arsenicals such as* atoxyl have been given

Tryparsamide is an efficient trypanocide Chesterman (1923) treated 40 cases in the Belgian Congo by 8 to 10 weekly intravenous injections of 3 gm each *dissolved in* 10 ccm of water with good results The dose should not exceed 4 gm and ...

Tryparsamide gives comparatively much better results than Bayer 205 in the treatment of trypanosomiasis when the central nervous system is affected It clears the blood in from 6 to 12 hours in doses of 1 5 gm intravenously in early infections due to *T gambiense* and the peripheral blood remains free for long periods sometime The drug is not effective in infections with *T rhodesiense*

Weekly injections of 2 to 3 gm in adults have been recommended because such doses give equally good results as large and more frequent doses and because they reduce the chances of ocular disturbance to the minimum In the first stage of the disease a total dosage of 20 to 50 gm suffices to produce a cure The blood and glands become negative there is marked clinical improvement in those cases in which the spinal fluid is only slightly changed before treatment and it tends to become normal with the treat ment In the second stage it is necessary to give 50 to 100 gm The patients who exhibit nervous and mental symptoms are said to show rapid and considerable improvement in cases of moderate intensity the benefit obtained is marked and constant The action is said to be rapid durable constant and is superior to other drugs Relapses or incomplete cures are always due to extraneous causes such as insufficient dosage irregularity of the injections and difficulties due to the patient Toxic reactions acute or chronic are negligible Blindness which occurs after treatment with tryparsamide is in most cases due to previous arsenical treatment Blindness does not usually come on suddenly and if patients are watched it is mostly transitory The premonitary symptoms are pain in eyeballs photophobia lacrymation and dimness of vision If these occur the drug should be stopped or the interval between injections lengthened The danger of blindness is increased as the cases are advanced and nearing death

Tryparsamide is said to have a beneficial effect on general nutrition in addi tion to its parasitotropic effects and some clinicians believe that its chief action is to build up the resistance of the body to combat infection

Tryparsamide has not been extensively used as a prophylactic drug in sleeping sickness in man In vaginal infections in animals (rabbits) it has a prophylactic effect

Arsenicals—Trypanosome infections were first treated with preparations of arsenic by Bruce (1895) and Lingard (1890) who employed them in animal trypanosomiasis Later Laveran and Mensil (1902) used inorganic arsenic in an attempt to cure trypanosomiasis

Atoxyl (soamin)—Atoxyl was employed by Koch (1907) in Africa in the treatment of sleeping sickness The preliminary reports inspired great hopes but later it was found that relapses frequently occurred while optic atrophy was by no means uncommon For details see the chapter on arsenic

Bismuth in trypanosomiasis—Colloidal bismuth and a basic oxy aminophenyl arsinate of bismuth have been tried but the results are not encouraging

Quinoline derivatives—Anil and steryl quinoline derivatives and surfen C have been tried in trypanosomiasis These compounds are of some use in animal trypanosomiasis only Clinical results have not been satisfactory

Acridine derivatives—Acriflavine has long been known to possess trypanocidal properties

The action of a number of pyrrole dyes has been tested (1935) on *T brucei* infections in *mice Pyrrole blue, pyrrol red and phthalocyanin have no trypanocidal action but the* perchlorate of a red dye obtained from Bacillus prodigiosus and termed prodigiosin was found to have a temporary curative action

Phenanthridinium compounds—Some phenanthridine and phenanthridinium compounds possess trypanocidal action and act on a strain of *T brucei* completely resistant to the largest tolerated doses of arsacetin

These compounds have been tried in trypanosomiasis

Bayer 9736 contains 22 per cent of arsenic and 5 per cent of sulphur The dose is 1 5 ccm of a 10 per cent solution to adult increased to 3 0 ccm It is given intravenously twice or thrice weekly till 50 ccm are given It is effective against T gambiense and T rhodesiense

3. Summary

Trypanosomiasis in man is a curable disease if it is early recognized and adequately treated Bayer 205 and tryparsamide are the two most effective drugs

[illegible]

Tryparsamide is given in doses 0 5 to 1 0 gm by the intravenous route at weekly intervals till 30 to 50 gm are given the course lasting 1 to 3 months In advanced cases it is advisable to give a small trial dose to test the sensitiveness of the patient to the drug The drug should then be rapidly pushed to its tolerence In cases where the central nervous system is affected a second course must be given after 1 to 3 months rest

Dosage for children up to 12 years is comparitively larger than for adults

Combined treatment with Bayer 205 and Tryparsamide is indicated in cases where the former fails

Evidence of cure are general improvement of the condition reduction of temperature, normal cell count and albumen content of the cerebro spinal fluid After treatment the patient should be examined every three to six months for 2 to 3 years

The antimony compounds have their chief application in veterinary practice

4. South American Trypanosomiasis

(Also known as Chaga's disease occurs in Panama Mexico, Brazil Argentine and other parts of South America)

The causal organism is the small C shaped *T cruzi* occurring sparsely in blood The disease specially affects children and acute and chronic forms have been described The parasite develops in the endothelial cells of *the body tissues especially heart internal* organs and striated muscle and destroys them There is rapid multiplication and formation of nests of leishmania which later develop into trypanosomes *These invade the blood* stream and occur as broad and slender forms

The parasite develops in the reduviid bug especially *Triatoma megista* now classified as *Panstronglus megistus* and also in *T infestans* in North Argentine The trypanosomes ingested pass through the gut and in 8 to 10 days fully develop metacyclic forms appear in the hind gut and pass out in the fæces Infection occurs when the bugs which are *vicious bite s* bite and defaecate in the wound Transmission in the bug is hereditary and parasites develop in larval and nymphal stage The domestic cat is infected and *under experimental conditions all laboratory* animals can be infected An animal named tatu Tatusia or *Dasypus novemcincta* whose body legs and tail have an armour is said to be *the host five species of this animal are said to be naturally infected with the parasites* Transmission is also said to occur through milk of infected mothers and through coitus

The heart is affected and enlarged, pericardial effusion and myocarditis are present the liver shows parenchymatous degeneration, the brain and cord show sub-serous echymosis and haemorrhages adrenals are also involved In acute stages there is high leucocytosis with increased mononuclears and severe anæmia

The severity of the disease varies in different localities In many cases in which the organism is found in the blood there may be no evidence of disease or of recent illness, though mild febrile disturbances may have occurred At the site of inoculation swellings Chagoma form and subsequently *metastatic tumours occur Unilateral opthalmia with* palpabral œdema and conjunctivitis *Romanos sign* is probably due to the entrance of *parasites through the conjunctiva The incubation period is between 7 to 14 days possibly* longer In experimentally infected human beings it was found to be 10 to 12 days

The acute type of disease is seen in children in the first year or two of their life There is fever rising to 104°F (40°C) œdema of face and unilateral conjunctivitis due to the bite of the infected bug The œdema may spread from the face to the rest of the body When flagellates disappear from the blood the temperature becomes normal There is general adenitis and the spleen and liver are enlarged death occurs from myocarditis produced by invasion of the heart muscle by the parasite Encephalo meningitis is a terminal event

... f the child recovers from the acute stage There is ...

Diagnosis depen ... the blood especially ... the febrile stage ... ood into susceptible animals ... xamina tion of muscles liver ...

Complement fixation test of Machado *with antigen* made from glycerine and water extract of heart and spleen of an infected animal is said to be specific Brumpts xenodiagnosis test *consists of an infection—free* Triatoma biting a patient its gut is examined after two weeks for the parasites Differential diagnosis from kala azar is important

Protection from bites of the bug by means of mosquitoe nets is the best prophylactic measure Bugs hide themselves in crevices roofs etc of the huts and are difficult to get at If possible destroy infected huts The bug is never found away from human habitation

Prog

Many deatl s occur in the acute stage in young children In adults cure may occur after the acute stage, but Chagas believes that the disease passes on to chronic stage In older children and adults infection produces mild symptoms Outlook in cases associated with endemic goitre is complicated

Treatm

Treatment is unsatisfactory with all drugs found favourable in African trypanosomiasis A number of new chemotherapeutic drugs of the amino quinoline series *e g* surfen C are very toxic and useless Bayer 205 (antrypol) undecaine I II diamidine arsenicals and antimonials atebrine are ineffective Bayer 7602 a quinoline derivative has been tried in Brazil and is said to have definite therapeutic activity The drug is given intramuscularly on alternate days as a freshly prepared 3 per cent solution in doses of 5 ccm for adults rising to 20 ccm a total of 22.2 mgm per kilo body weight is sufficient to effect a cure Five injections are given on alternate days The drug is said to reduce leishmanial figures indirectly by direct action on trypanosomiasis

Bayer 9736 is another drug which contains 22 per cent of arsenic and 5 per cent of sulphur It is less toxic than 7602 and is given intravenously in 10 per cent solution The adult dose is 1 5 ccm (0 15 gm) increasing to 3 0 or even 4 5 ccm given twice or thrice weekly to a total of 50 ccm (5 0 gm) for men 40 ccm for women and 30 ccm for children

M3024 I C I is the British equivalent of Bayer 7602 Initial dose 7 12 mgm per kilo usually 0 15 gm 2 to 4 ccm given at 5 7 days intervals the second dose being double of first Improvement is said to be rapid Penicillin used locally and intramuscularly and a total 4 to 5 hundred thousand units gives good results

Rats recovered from the disease are immune to re infection Administration of serum of recovered animals does not prevent infection but reduces the severity of symptoms and reduces the number of trypanosomes in the blood

When the disease is complicated with myxoedema treatment for the latter condition should be given

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CHAPTER III

LEISHMANIASIS

Kala-Azar

CLINICAL ASPECTS—DIAGNOSIS—SPECIFIC TREATMENT ANTIMONY DERIVATIVES ANTIMONY COMPOUNDS ACTION OF ORGANIC ANTIMONY COMPOUNDS—ANTIMONY IN VISCERAL LEISHMANIASIS PENTAVALENT COMPOUNDS ANTIMONY RESISTENCE EVIDENCE OF CURE—MODE OF ACTION—ROUTES OF ADMINISTRATION—TOXIC EFFECTS—SUMMARY—AROMATIC DIAMIDINES—TREATMENT OF RESISTANT CASES—TREATMENT OF COMPLICATIONS—TREATMENT OF POST KALA AZAR DERMAL LEISHMANIASIS

Cutaneous Leishmaniasis

ORIENTAL SORE—MUCO-CUTANEOUS (SOUTH AMERICAN LEISHMANIASIS)—LEISHMANIAL DYSENTRY

General Consideration

The term *Leishmaniasis* includes a number of conditions occurring as a result of infection with various species or varieties of species of genus Leishmania namely —

1 *Visceral Leishmaniasis*

(*a*) *Indian Kala azar* caused by *L donovani* which spreads by the blood stream into all the body tissues except the nervous system

(*b*) *Infantile kala azar* caused by *L infantum* which has now been shown to be the same as *L donovani* *L chagasi* which produces South American Kala azar is also indistinguishable from *L donovani*

2 *Cutaneous Leishmaniasis*

Oriental Sore The causal organism is *L tropica* which usually does not spread by blood stream

3 *Muco cutaneous Leishmaniasis*

Espundia The causal organism is *L. braziliensis* which spreads from a primary invasion of the skin after it has healed to nasal buccal and pharyngeal mucous membranes

4 In addition dermal leishmaniasis may occur as complication or as a sequel to Visceral Leishmaniasis particularly as a post kala azar condition after treatment with antimony compounds

According to some workers there is no hard and fast line of demarcation between these types Thus in Kala azar there is a primary skin lesion which instead of leading to permanent healing and solid immunity as in case of oriental sore leads to the generalized disease Kala azar Similarly in muco cutaneous leishmaniasis the primary lesion occurs on the skin which may behave like oriental sore in some cases *while in others secondary* lesions in mucosa of the nose mouth and pharynx may develop Transition forms in between the three clearly defined types of leishmaniasis are seen

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This section is largely based on the classical work of Dr L E Napier on leishmaniasis in India as summarised in his Principles and Practice of Tropical Medicine 1943

KALA-AZAR

Kala azar is an infective disease characterised by persistent fever leading to enlargement of spleen and liver and cachexia The disease is widespread in many parts of Asia In Europe it occurs in countries bordering on the Mediterranean it is prevalent in parts of

Epidemiolog

Kala azar is endemic in Bengal and Assam here it was subject to exacerbations of epidemic like nature which had a definite period city On account of extensive treatment campaigns the character and periodicity of these epidemic waves is being disturbed both in Assam and Bengal The disease may show true epidemic invasion in an area and three of these epidemics have been recorded in Assam during the last fifty years

Kala azar is usually confined to areas below an altitude of 2 000 feet and prefers alluvial soil and a mean annual hum dity of not less than 70 per cent with a low mean diurnal range of temperature of not less than 20°F It is a disease of rural areas rather than towns It is a fam ly house and s te infection

There is definite seasonal incidence and in Bengal and Assam there is a peak in the winter months but it starts to rise in the autumn during the period immediately following the rainy season

Europeans and Anglo Indians

Aetiology

The disease is
Leishman a—L do
the Leishman Don
occuring in its art
The L D body
parts of the body
and submucosa of
endothel al cells
being phagocytosed
The leishmania m
parasites may occur n a single cell Parasites have also been found in the urine and fæces

duced by subcutaneous peritoneal or oral routes

Transmissio

The sandfly *Phlebotomus argentipes P major var chinensis* and *P perniciosus* are

The sandfl es are found in the ground floor rooms of houses w th unpaved floors which are damp and badly ventilated and in cattle sheds They breed in any earth that contains admixture of nitrogenous matter They prefer to feed on cattle and bite man when these are not available In the laboratory the sandfly breeds at a constant temperature of 80° to 82°F

It is believed that in India man is the main source of infect on and the patients treated and cured of the d sease may still be source of infection In the Mediterranean area and

China infected dogs may act as carriers In India canine infection occurs in Northern India where Kala azar does not occur (Napier)

Natural immunity in Kala azar does exist that there is acquired immunity is evident from the fact spontaneous cures occur in this disease There also appears to be little doubt that there is gradual development of immunity established by previous infection recorded in dogs after cure It has been shown that there are differences in the antigenic structure of *L donovani* *L tropica* and *L braziliensis* but *L infantum* was antigentically identical

General lowering of resistence is an important factor in contracting the disease and debilitated individual are usually picked out In epidemics of Kala azar in India circumstances which have periodically lowered the general vitality of the people have been determining factor

The parasites occur in all parts of the body in areas rich in reticulo-endothelial cells Macrophage proliferation actually preceeds parasites and all changes observed in different organs are due to proliferation of reticulo endothelial tissues the fibrotic changes occuring in organs such as the liver and spleen appear late and are not constant (Napier) The spleen is generally enormously enlarged and may weigh 8 to 10 lbs or more There may be perisplenitis and thickening of the capsule its consistency is not hard (like malaria) and it is friable the cut surface is uniformly dark red there may be infarcts

Histologically there is infiltration with heavily parasitized macrophages which dominate the picture they encroach into the Malpighian corpuscles which completely disappear the vascular spaces are enlarged

The liver is enlarged firm friable and has a greasy look as in fatty degeneration Kupfer s stellate cells are enlarged and parasitized and proliferated especially in the portal zone and portal spaces In the central zone the capillaries are dilated and both the liver cells and the reticulo endothelial cells are atrophied and fatty changes are present in them

In the intestines proliferation and parasitization of reticulo endothelial cells may occur in the submucosa

In post Kala azar *dermal leishmaniasis the subpapillary layer is œdematous and the* vessels are enlarged, dilated and infiltrated with macrophages Parasites do not occur in early lesions in large numbers they occur in the cutaneous nodules

The blood shows a red cell count of about 2 to 3 millions reticulocytes are above normal (2 to 4 per cent) and the fragility of red cells is decreased to hypo and hypertonic saline solutions The leucocyte count is usually below 4,000 per ccm normal ratio of *1 750* red cells being reduced to 1 1000 to [illegible] rarel seen eosinophils are usually 1 to 2 per cent there ma [illegible] nuclears There is decrease in blood platelets to [illegible] reduced from 5 minutes to about 3 The sedimer [illegible] ean reading was *65 3+11 2 mm* The pH of the b [illegible] serve is reduced and so is the blood calcium the [illegible] ent there is an inversion in the albumin globulin [illegible] tment There is nearly always a trace *of albumin and marked increase in* urobilin in the urine (Napier)

1. Clinical Aspects

The incubation period is usually between six weeks to four months but cases have been recorded *in which it has been as short* as 10 to 14 days or as long as 18 months A case of congenital infection has been reported

The onset may be acute or insidious In India it may be enteric like or malaria like There is general malaise and the temperature rises rapidly up to 103 to 104°F in a week or so this is maintained for a week or 10 days and then gradually falls to 99°F or even to normal The temperature *assumes the form of* long irregular waves it may remain low for a week or so and then gradually goes up again The double diurnal rise is observed in less than 10 per cent of the cases in some there is a third diurnal rise to demonstrate this temperature has to be taken every *three hours In the second* febrile attack the temperature may be remittent or intermittent and the classical double rise may appear The spleen is palpable pulse is 120 per minute and the patient is not toxic

In the malaria type the onset is more acute and fever may be accompanied by a rigor this fever may even respond to quinine during the first attack but not so much in the second attack and afterwards

In the insidious type the time of onset cannot be determined but the patient gets attacks of irregular fever and comes to the hospital with an enlarged spleen with some such complications as dysentery or pneumonia the condition is discovered accidentally The serum test shows that the disease is in an advanced stage

Cases are met with transient infection the parasites being demonstrated by blood culture but symptoms subside even if no treatment is given these patients may not return for 3 or 4 years with any symptoms of disease (Napier)

Signs and Symptoms

When the disease is established and has progressed for six months or so there is fever with progressive loss of weight weakness increasing pigmentation in the skin falling of hair shortness of breath palpitation attacks of diarrhœa bleeding from the gums and irritating cough The patient may look well nourished or emaciated and there is dark pigmentation of the skin in the region of the forehead and around the mouth the hair is dry lusturless and sparse and may entirely disappear There is visible pulsation of the carotids in the neck the abdomen is prominent on account of the splenic enlargement which is a most constant feature The peculiar soft doughy consistency of the spleen is characteristic of Kala azar except in rare cases when it may be hard There is usually some enlargement of the liver Jaundice is not common in the early stages of the disease but may be present later (Napier)

The typical fever is present but apyrexial cases may occur Even with a temperature of 102°F or more symptoms are slight and the patient may be doing his work in the ordinary way Headache may be present but is usually not severe no mental dullness is present Retinal haemorrhage may occur

The blood pressure is usually low about 100 mm systolic pulse is 100 to 120 per minute The heart shows some dilatation or may even hypertrophy haemic murmers are frequently present oedema of extremeties is common Ascites may occur in a small number and is a bad sign from the point of view of prognosis Bleeding from the gums and epistaxis commonly occur appearance of purpuric spots is uncommon and is a terminal symptom it may be accompanied by uncontrollable hæmorrhage from the gums and the intestines retinal haemorrhages rarely occur

Gingivitis with loosening of teeth is common and cancrum oris is not uncommon during the late stages in fatal cases

Diarrhœa and dysentery are common complications and a specific leishmanial dysentery has been described a terminal dysentery may occur In later stages congestion of lungs and broncho pneumonia may occur The nervous system is not affected in this disease and the patient is mentally quite clear even in the final stages Herpes zoster may sometime occur

There is no renal insufficiency and such symptoms as swelling of the legs and puffiness of face may be due to vasomotor disturbances In women amenorrhoea is an early symptom an uncomplicated pregnancy may go on to full term (Napier)

Sequelae

After proper treatment most cases recover completely post kala azar dermal leishmaniasis being the only sequel of importance This condition occurs in about 6 per cent of cases in old endemic areas of Kala azar after full treatment with antimony compounds It is believed that in a number of cases leishmania persists in the skin after cure of the visceral infection This is of epidemiological importance Usually about a year but sometime several years elapse before the dermal infection is manifested

Post Kala a[illegible] Dermal leishmaniasis

It has no relation to the oriental sore Hypopigmented macules may occur on the trunk, arms thighs legs abdomen which may resemble leucoderma, but the depigmentation is never so complete The butterfly erythema may occur on the face nose cheeks and chin the area involved being photosensitive Nodules may occur on the face lips forehead etc and may be mistaken for leprosy they rarely ulcerate

Complications Lowered body resistance may produce bacterial invasion resulting in cancrum oris septicæmia pneumonia cystitis otitis etc anæmia and agranulocytosis may

occur Diarrhœa and dysenteric symptoms *may* be *produced* by influx of the parasites into the intestinal mucosa and secondary infection of the ulcers is thus produced

2. Diagnosis

In endemic areas diagnosis can be made from the clinical picture but it can only be established on demonstration of the parasite *Splenomegaly* irregular pyrexia, bleeding from nose and gums anorexia, loss *of strength emaciation* pigment spots cancrum oris, etc give indication of the disease Leucopenia is an important positive therapeutic test, *i e* response to a few injections of antimony is not dependable and therefore, not justified because it takes a long time before the cases show improvement under antimony treatment. However quinine *proving ineffective in reducing fever* may prove useful In view of

the diagnosis made on clinical

ll practical purposes when the

e demonstration of *L donovani*

al proof of the disease and is

necessary in early cases of kala azar

Repeated examination of blood films made with special care to get a straight leucocytic edge *and stained by Leishman or Giemsa's* stains will help in establishing diagnosis in 60 to 70 per cent cases An intravenous injection of an organic antimony compound increases the chances of finding L D bodies provided the film is prepared within half an hour of the injection (Chopra and Dasgupta)

Under very strict aseptic precautions blood is taken from a vein and about 0 5 ccm is added to 10 ccm of saline containing 2 per cent sodium citrate The cellular deposit after setting is then sown into NNN medium (rabbits blood agar slope with condensation fluid) *the tubes* are incubated *at 20 to 24°C for at least* a week, and drops of the condensation fluid are examined at intervals in a fresh state in positive cases flagellates are seen moving about amongst the red corpuscles Cultures however can not be discarded before a month If proper care is taken the results are successful in almost all cases (Napier)

Spleen puncture is the most important method of diagnosis and if performed with reasonable care in properly selected cases is not at all a dangerous procedure particularly in experienced hands

Calcium lactate 30 gr is given the previous night in two ounces of water and again next morning no food is allowed The puncture is done with a 5 ccm syringe and No 11 needle about 1 to 1½ inch in length The patient lies flat on his bed and the operator sits on the edge of bed on the left of the patient A point is selected half an inch below the costal margin about the centre of the parietal surface of the spleen After carefully sterilizing the skin at the site of puncture with pure phenol which is wiped off with a spirit swab a puncture is made in two movements with the first movement the skin is punctured and with the second the needle is plunged into the organ After *puncturing the skin* the direction of the angle of the needle is charged to an upward and outward direction paralell with the long axis of the spleen and at an angle of 45° with the skin surface The needle is then plunged into the spleen and the piston is withdrawn rapidly two or three times the needle is then withdrawn altogether The contents of the needle are put in a slide and into the culture medium A special *attachment which can* be held and worked single handed has been devised After the puncture a binder is applied and calcium lactate 30 gr is given the patient rests in bed for the day and is allowed food one hour after the puncture Spleen puncture according to Napier is the sheet anchor of diagnosis in Kala azar and gives 95 per cent positive results *by smear and 100 per cent* by culture (Napier)

Liver puncture according to some is less dangerous but parasites are difficult to find it is now discarded in favour of sternal puncture *The best site for sternal puncture is* just on one side of the middle line at the level of the second intercostal space A Salah needle of rustless steel is preferable and an 18 gauge lumber puncture needle may be used Usually a guard has to be *fixed at a distance* of 1 to 1 5 cm The skin is first cleaned and the subcutaneous tissue is infiltrated *with a 2 per cent solution of novocaine* or percaine the bone is then pierced with a rotary movement often considerable force is necessary when the marrow cavity is reached there is loss of resistance The stylet is then taken out and with a 2 ccm record glass syringe aspiration is made When the fluid is aspirated the patient *has a dragging pain which shows* that the needle is in the marrow cavity Only a few drops of the blood are removed the needle is withdrawn and

digital pressure applied over the puncture which is then sealed A smear is then made on a slide and NNN tube inoculated It is only rarely that there is failure to obtain blood and this is usually due to the needle being too short (Napier)

Tibia puncture is made in case of young children (where the sternum is soft) in the middle of the shaft with the sternal puncture needle The percentage of positive results is smaller than with sternal puncture

Formo gel or aldehyde reaction

For the Formol gel or aldehyde reaction 40 per cent formaldehyde is added to 1 ccm of suspected serum in a test tube The mixture is then shaken in a few minutes the serum will solidify and then becomes opaque the degree of opacity being the criterion for the test being positive the test should be read after 24 hours In early stages of the disease the test is negative and it gradually disappears progressively during convalescence The test is negative in cutaneous leishmaniasis Partial solidification may occur in tuberculosis leprosy, and syphilis and chronic malaria but serum does not become opaque

Chopra's antim test (serum te Finger prick blood test

Whole serum and serum diluted 1 in 10 with distilled water are put in miniature test tubes (2½ to 3 inches long made by sealing one end of a piece of glass tubing 4 to 5 mm in diameter), with a capillary pipette A 4 per cent solution of urea stibamine made with distilled water is then slowly run along the side of the tubes A heavy coarsely flocculent precipitate forms when the antimony solution comes in contact with the serum Tartar emetic does not give this reaction but stibosan does In very early cases 1 in 10 dilution of the serum may give negative results and whole serum should be employed A correct diagnosis can be made by this test in 88.2 per cent of cases as compared with 83 5 per cent of the aldehyde test

Chopra reaction

For [illegible]
test tube [illegible]
solution [illegible]
formed v [illegible]
the same [illegible]
should b [illegible]
in 86.4 [illegible]

[illegible]

Mix one part of serum in two parts of distilled water A turbidity and later a flocculent precipitate develops in positive cases If water is poured on the surface of the serum a ring effect is produced This test is due to a marked increase in the euglobulin content of the serum

Diagnosis of post Kala azar dermal leishmanoid is easily made by the typical hypo pigmented macules and the erythematous rash A nodule snipped off with a pair of scissors and a smear on a slide is made by rubbing the cut surface on staining parasites are found in the endothelial cells or in a free condition in positive cases

Prophylaxis

In India no animal reservoir of infection has been found and man is always the source [illegible]
blood The [illegible]
with dermal [illegible]
be prevented from breeding The control of sandflies in rural area is very difficult Paving of floors helps, holes, cracks or fissures are sprayed with kerosine oil emulsion It has been shown that sand flies prefer bovine to human blood but is doubtful if proximity of cowsheds etc, will attract these and save man Sandflies are sensitive to smoke and their range of flight is short, they do not breed in the open and their larvae could be destroyed by spraying with some antiseptic in the possible breeding places

Prognosis

In untreated cases in India the mortality ranged between 75 to 98 per cent and the mortality in infantile form was the same The fever lasted for a year

or longer, the high remittent fever being followed by complete absence of fever for a month or two. After a total period of about two years, some cases assumed a chronic form with no fever but with anæmia and enlarged spleen, others ended fatally. Death is caused by some complication, e.g., dysentery, pneumonia, cancrum oris, etc. In children the disease runs an acute course, death often occurring in about six months. If full treatment with antimony is given between the 3rd and 12th month of disease, 85 to 90 per cent of cases recover. Of the number that relapse, two third are subsequently cured by proper treatment. If the disease has lasted for more than a year the patient may become weak and emaciated and is liable to get complications, such as cirrhotic liver, jaundice and ascites, ending fatally.

3. Specific Treatment

(1) Antimony and its Derivatives

Antimony has a very interesting history. Grey antimony has been used from the earliest times in the East as an 'eye salve' for protection against endemic eye diseases and as a remedy for oriental sore. In the 16th and the 17th centuries antimony was considered as a panacea for many diseases, e.g., syphilis, leprosy, plague, cancer, ague, perhaps a forecast of its most recent use in chemotherapy. As early as 1631 the preparation antimony tartrate or *tartar emetic* came into existence and by the end of the 17th century more than a hundred preparations of antimony were in use in medicine chiefly against plague and other infectious fevers. Owing however to its indiscriminate use many deaths occurred and it was discarded to a great extent and in many places its use was actually prohibited.

The modern development of antimony therapy began in 1907 following the work of ... [illegible] action of tartar

which can be administered readily [illegible]
effects so that the therapeutic effects are rapidly attained.

(2) Pharmacological Action

The action of the antimony ion in the main resembles that of the arsenic ion, the chief differences lying in its stronger local irritant effects and more difficult absorption.

Action on protozoa. The salts of antimony, arsenic and bismuth have been shown to have special affinity for certain pathogenic protozoa. Antimony destroys trypanosomes in drawn blood in such high dilutions as 1 in 500 000. The non pathogenic protozoa such as the paramœcium are not affected even by concentrations of 1 in 5000. It would appear therefore that these compounds have a specific effect against certain pathogenic protozoa in the same way as quinine has against the malarial parasites.

Externally. When rubbed into the skin antimony salts produce a characteristic inflammation at first papular then vesicular and lastly pustular. The rash looks like the eruptions of smallpox. Given subcutaneously the salts give rise to severe pain and inflammation

Internally When given by the mouth tartar emetic has an acrid metallic taste and

Absorption and distribution

In the stomach antimony produces irritation As a rule vomiting removes the compound from the stomach and very little passes into the intestines but when it does it produces diarrhœa and colic Absorption of antimony is very slow from the skin or from the gastro intestinal tract As it is too irritating to be administered by subcutaneous or intramuscular routes the intravenous route is the only possible one Fortunately the toxicity of these compounds when given by this route is very low as large amounts are rapidly excreted by the kidneys From the blood antimony passes into the tissues much more slowly than arsenic It is found in considerable quantities in the liver kidneys and intestines come next but contain smaller quantities The other organs only show small amount of the metal The volume of both the liver and the spleen is considerably increased after intravenous injections

The distribution of antimony in the system depends to a large extent on the quantity administered after gradual administration of small doses considerable quantities are only found in the liver which stores antimony and in the kidneys which excrete it Like arsenic, antimony gradually accumulates in the hair and nails

Circulation

The cardio vascular effects produced by antimony resemble those produced by arsenic but acceleration of the pulse seen after tartar emetic is a reflex effect due to the emetic action and not to the absorption of the antimony ions When injected into a vein antimony acts directly on the cardiac muscle and capillaries producing a slow and weak pulse the heart muscle is depressed the capillaries are dilated There is paralysis of the walls of the arterioles due to its direct action on the muscular coat the vessels of the splanchnic area are particularly affected The blood pressure falls on account of vaso motor paralysis tachycardia may occur and may be distressing The heart becomes weak and rapid at first and is later slowed the contractility of the cardiac muscle is eventually destroyed and the heart stops in diastole

The alkalinity of blood and the number of erythrocytes are said to decrease while the leucocytes are said to be increased Tartar emetic and organic antimony compounds do not hæmolyse or agglutinate erythrocytes either *in vitro* or *in vivo* In maximum doses it produces leucopænia in the peripheral blood and increased phagocytosis in the spleen

After the injection of trivalent antimony preparations bradycardia of short duration setting in immediately after injection and a prolonged retardation of the pulse which gradually develops in the course of the injection series have repeatedly been reported

Respiration

There is slight initial acceleration but soon there is nausea and the respiration becomes shallow and irregular In cases of poisoning respiration is very slow laboured and finally ceases along with the stoppage of the heart Intravenous injections stimulate the respiration slightly large doses produce marked congestion and œdema of the lungs in fatal cases of poisoning

Secretions

The secretions such as perspiration saliva mucus sputum bile etc are increased The quantity of urine is increased with small doses with large doses it is decreased and may even be suppressed

Metabolism temperature

The effects of antimony on metabolism have not been studied so thoroughly as those of arsenic but antimony compounds seem to present a strong resemblance to the arsenicals Prolonged use of toxic doses produces fatty degeneration of many organs probably owing to diminished oxygenation and metabolism Antimony salts have a distinct antipyretic effect Vomiting is also accompanied by a fall of temperature which may amount to 1°C (1 5° to 2°F)

Central nervous system

In the frog subcutaneous injections of the double tartrates produce initial stimulation of the medulla followed by paralysis Later the spinal cord and the motor ganglia of the brain become paralysed and the reflexes are lost It has a depressing effect on the nerve cells

Antimony salts are mainly excreted by the stomach, the intestines and the kidneys, traces occur in the bile, the sweat and in the milk, and possibly also in the bronchial secretion There is less danger of cumulative poisoning than with arsenic since antimony [illegible] more rapidly excreted. After intraveno[illegible]
of antimony is excreted in the [illegible]
1 0 gm was recovered from the [illegible]
from urine in 6 to 12 days [illegible]
the fæces It should be used wit[illegible]
the circulatory and the respir[illegible]
inflammation of the kidneys acc[illegible]
kidney substance

Much of the antimony is excreted in the case of the organic compound by the kidneys within a few hours of administration, and a large proportion of the pentavalent compounds remain pentavalent only a part being reduced to the trivalent state in the body

(3) Action of Organic Antimony Compounds

The pentavalent organic antimony compounds all contain antimony in strong linkage. They have no local irritant effect and only cause slight toxic effects, they are much less toxic than trivalent antimony compounds Their effects on the circulation are similar to those of the stable trivalent compounds

Chopra (1927) showed that the action of the organic compounds of antimony such as urea stibamine is in the main the same as that of the antimonyl tartrates Intravenous injections of most of these compounds produce a fall of blood pressure which is often more marked than in the case of tartrates The heart becomes slow and irregular but it gradually recovers and the blood pressure comes to its normal level All these compounds have a depressant action on the heart and relax the ventricles in the same way as cinchona alkaloids There is a marked rise of pulmonary pressure The arsenical compounds such as salvarsan also cause a marked rise of pulmonary pressure Acute toxic symptoms resembling 'nitritoid crisis' are rare with the tartrates but they are not uncommon when organic compounds are administered

On the spleen and the liver the effect of these compounds is noteworthy In experimental animals there is a well marked increase in the volume of the spleen accompanied by increase of rhythmic movements The same is the case with the liver though the effect is not so apparent The effects produced are more marked in case of the organic compounds than with the antimonyl tartrates After injections of antimony compounds in human subjects the patients often complain of a feeling of pain and a sensation of distention in the splenic region and there may also be uneasiness in the hepatic region These can be accounted for by the increase in the volume and rhythmic movements of these organs It is possible that this increase has something to do with the therapeutic effects produced by these compounds The spleen and the liver act as reservoirs of parasites and the influx of blood charged with antimony into these organs may contribute towards the destruction or expulsion of the parasites from these hiding places It has been found that soon after injections of an antimony compound Leishman donovan bodies make their appearance in the peripheral blood where they were previously absent showing that the action is of a provocative nature

Antimony has a stimulating effect on the adrenals It has been shown by Chopra and his collaborators (1928) that the residual epinephrine contents of the supra renal glands of rabbits who have had a course of antimony compounds is higher than those of normal animals

Tolerance to arsenic does not confer tolerance to antimony Some of the infusoria become resistant to the action of antimony

The maximum tolerated dose of tartar emetic for rats rabbits and guinea pigs by slow intravenous injection of a 1 0 per cent solution is about 0 015 gm per kilo body weight For a man of 70 kilos (145 lbs) it corresponds to 1.05 gm, the dose usually given to human beings at one time, i e, 5 to 10 ccm of a 1 0 per cent solution (0 5 to 0 1 gm) is therefore well within the range of safety Such a dose would be 10 to 20 times smaller than the maximum tolerated dose and it may be safely repeated Cases of poisoning are due to increased susceptibility of individuals and deaths have occurred from 2 grain doses given intravenously It is therefore advisable to start with such small doses as 1 to 2 ccm

pentavalent aromatic organic compounds

The symptoms of acute poisoning resemble those of arsenic these generally begin with nausea vomiting and pain in the stomach which is not relieved by vomiting Emesis is violent and continuous and may contain blood Vomiting is accompanied by profuse diarrhœa followed by great muscular weakness and collapse The pulse and the respiration become slow and irregular the skin is cold and covered with perspiration, cyanosis of the face and extremities is generally marked and the temperature is subnormal The patient falls into a comatose condition

Poisoning in man

Chronic poisoning is rare and difficult to diagnose It has been observed in type setters and is usually mistaken for plumbism The pentasulphide is used in the manufacture of rubber, and antimony salts are also used in glazing cheap granite ware, and in this way may contaminate food stored in them Since antimony compounds have come into vogue in the treatment of tropical diseases symptoms of chronic poisoning are sometimes seen *These symptoms are loss of appetite depression headache giddiness, anæm a confusion* drowsiness and dimness of vision The patient complains of a feeling of suffocation or a feeling of spasm of the glottis discomfort or pain in the region of the stomach general weakness and exhaustion Profuse d arrhœa may ensue and ulceration of the small intestines The blood pressure is low and the blood shows leukopænia and eosinophilia There may be rapid loss of flesh dysuria, albuminuria, transient jaundice and paraplegia

Preparations of Antimony

Like many metals antimony forms two series of compounds, its valency varying from three to five

Antimony compounds may be classified as —(1) Inorganic salts (2) Organic salts, *e g*, antimonyl tartrates (trivalent salts) (3) Organic compounds (*a*) Trivalent, many of these are unstable (*b*) Pentavalent, these are stable and are commonly used

(*a*) *Trivalent*

The inorganic compounds are not used in therapeutics Metallic antimony in a fine state of subdivision as an impalpable powder, colloidal antimony and antimony sulphide in a colloidal state, have been used by intramusclar injections in leishmaniasis and other protozoal affections, but their therapeutic action is doubtful

The organic salts or the trivalent compounds Antimonium tartratum or tartar emetic' is potasium antimony tartrate contains 36 5 per cent of Sb

Antimonyl Tartrates

Sodium antimonyl tartrate was originally tried by Thomson, experiments on pigeons and rabbits showed that the sodium salt is less toxic than tartar emetic The therapeutic effects of this compound are the same as 'tartar emetic' It is also known as 'stibinol' and contains 38 3 per cent of Sb

An alkaline solution of sodium antimony tartrate known as 'neostibinol' is less toxic and equally effective

Aromatic compounds of antimony (*a*) Trivalent A large number of antimony analogues of the organic arsenicals have been prepared The trivalent compounds, *i e*, the analogues of salvarsan are not very stable

Organic aromatic Compounds

The highly irritative action and toxic properties of tartar emetic are essentially due to

musculariy and which showed a surprising increase in the chemotherapeutic index against trypanosomes

The potassium salt was subsequently replaced in further developments by the sod um salt sodium antimony III bispyrocatechol 3 5 sodium disulphonate to which the name of *fouadin or neo antimosan* was given The concentration of the solution is increased and adapted to isotony with the tissue fluids 1 ccm contains 63 mgm of fouadin substance=8 5 mgm Sb III whereas antimosan contained 50 mgm antimosan substance=6.25 mgm Sb III The increase of the concentration simultaneously produces the advantage of a smaller injection volume With a pH close to 7 it was possible to adjust the solution for injection to the pH of the tissue fluids this makes intramuscular injections painless The antimony oxide used in the production of fouadin is subjected to a special purifying process in order to remove traces of lead etc which proved especially harmful with tartar emetic.

The solution of fouadin in ampoules is sensitive to air A stabilised solution is used in bottles The drug is sold in ampoules containing 3 5 and 5 ccm (1 cc contains 0 064 gm of fouadin)

Fouadin Concentrate—The calcium sodium salt of antimony III pyrocatechind sulphonic acid has a peculiarity in that the isotonic solution has a higher concentration (1 ccm=14 3 mgm SbIII) than the sodium salt (fouadin 1 ccm=8 5 mgm SbIV) The injection volume is thereby reduced by two fifths which seemed to be an advantage from the point of view of intramuscular injection Moreover pharmacological considerations favoured the introduction of calcium

On account of the increased antimony content mentioned above, 3 ccm (=42 9 mgm SbIII) of the isotonic solution of the preparation correspond in so far as its antimony content is concerned to the usual full doses of fouadin (5 ccm=42 5 mgm SbIII)

Toxicity tests on mice with intravenous and subcutaneous injections showed that the toxicity in regard to antimony is the same as in fouadin

Anthiomaline is lithium antimony *thiomalate which contains 16 per cent of antimony It* is prepared as a 6 per cent solution and its dose is from 0 5 to 2 0 ccm (1 ccm=0.01 gm Sb) it is given intramuscularly and a course of 12 to 20 injections is given at the rate of 2 to 3 injections in a week It has a low toxicity and has been used in the treatment of schistosomiasis granuloma inguinale and leishmaniasis

Pentavalent Of the antimonials the various pentavalent compounds containing p amino phenyl stibonic acid *viz* urea stibamine and similar urea compounds neostibosan or diethyla mine p amino phenyl stiborate and sodium antimony gluconate are the most successful ... The present

The sodium salt of p amino phenyl stibinic acid or sodium p-amino phenyl stibinate is also a soluble compound which though therapeutically active is unfortunately not very stable Brahmachari ... stibinic acid This subst... urea ... urea

Von Heyden introduced a compound metachloro para acetyl amino phenyl stibinate of sodium (chloro stibacetin or von Heyden 471) under the trade name of stibosan They *Stibosan*

Table of Preparations of Antimony Compounds

(Modified from "Advances in Therapeutics of Antimony By Schmidt H and Peter F M 1938)

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	Trivalent Preparations			
1	Tartar emetic	Tartarus stibiatus Tartarus emeticus	Antimony tartrate of potassium	36 5 per cent
2	Sodium antimony tartrate	Stibyal Stibnal Neostibnal S A T	Antimony tartrate of sodium	38 3 per cent
3	(Old) Antimosan	Potassium Antimosan 661	Antimony pyrocatechin d sulphonate of potassium (D 12 5 % Sb)	D) 1 ccm=6 25 mgm
4	Fouadin (Neo antimosan)	Sodium antimosan Sdt 91	Antimony pyrocatechin disulphate of sodium (D 13 5 % Sb)	D) 1 ccm=8 5 mgm
5	Anthiomaline	110 L	Antimony thiomalate of lithium	D) 1 ccm=10 mgm

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... amino ... tethyla ... cessful ... present

Triarylstibines were first prepared ... development of organic antimony derivatives is mostly due to the work done by ... into the aromatic nucleus the ... and most of the antimony ... were prepared From ...

stibinate was ... series to be used in the treatment of leishmaniasis ...

The sodium salt of p amino phenyl sti... also a soluble compound which though stable Brahmachari (1922) prepared the ...

The combination of urea with p-amino-phenyl stibinic acid renders the latter compound more stable and soluble (p amino-phenyl-stibinic acid is *not soluble*) and at the same time it is more efficacious therapeutically It is a well known fact that when *quinine* is combined with urea, its solubility and diffusibility are considerably increased, and the resultant compound is able to penetrate better into the tissues its local anæsthetic action is also much enhanced Similarly better penetrability of these compounds probably accounts for the superior therapeutic results obtained by them as compared with the previous compounds

Von Heyden introduced a compound metachloro para acetyl amino phenyl stibinate of sodium (chloro *stibacetin* or von Heyden 471) under the trade name of stibosan They later introduced two other compounds *diethylamine* para amino phenyl stibinate (von Heyden 693) and neostibosan (von Heyden 693 B) Both these *compounds* are much more effective than the earlier organic aromatic compounds and are at least as effective as *urea* stibamine *Neostibosan* is not available in India at present but it is being prepared in America so supplies may become available in near futures

Stibamine has also been combined with glucose and a preparation stibamine glucoside also known as 'neostam' is on the market A compound *p* amino-phenyl stibinic acid combined with urea and glucose sold under the trade name of amino-stiburea Most of the antimony compounds in use at present are not very stable in the air even in a solid condition and in solution some of them change very rapidly

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5 Anthiomaline	110 L	Antimony thiomalate of lithium	D) 1ccm=10 mgm

Pentavalent Preparations

1	Stibenyl	Stibacetin	p acetyl amino phenyl stibinate of sodium	D) 33 per cent
2	Urea stibamine	Ureastibol Stiburea	p carbamino phenyl stibinate of ammonia (?)	About 35 per cent (?) (Data & results vary)
3	Stibosan	471	m chlor p acetyl amino phenyl stibinate of sodium	D) 31 per cent
4	Neostam	Stibamine glucoside	nitrogen glucoside of p amino phenylstibinate of sodium	About 30 per cent
5	Amino stiburea	Urea stibamine glucose	p amino-phenylstibinic acid combined with urea and glucose	24 8 per cent
6	Neostibosan	693 B	diethyl p aminophenyl stib nate of diethyl amine	D) 42 per cent
7	Solustibosan	Sdt 561	Antimony hexonate	1 ccm=20 mgm Sb

D) denotes that in these cases the antimony content is that stated by the manufacturers whereas the remaining data are obtained from literature

Table of Toxicity of Antimony Compounds

Name		Minimum lethal dose in mgm per kilo of mice	Maximum tolerated dose in mgm per k lo of mice	Percentage of antimony
Potassium antimony tartrate	—	16	—	—
Sodium antimony tartrate	—	20	—	—
Stibacetin and stibenyl	—	133	—	33
Urea stibamine Stiburea *Ureastibol* —	—	250	175	20—43
Stibosan or von Heyden 471	—	275	200	31
Stibamine glucoside Neostam	—	500	300	30
Aminostiburea —	—	250		24.8
Von Heyden 603 & 693 B *Neostibosan*	—	350	— 250	40

The pentavalent compounds can now be therapeutically tested on the striped Chinese hamster *Cricetulus griseus* or the *European hamster Cricetulus frumentarius both of which* can be easily infected with leishmania The chemotherapeut c index of some of the com pounds is as follows —

Antimosan 1 5 Stibosan 1 5 to 1 7 and Neostibosan 1 50

4. Antimony in Kala azar or Visceral Leishmaniasis

Before the introduction of intravenous injections of antimony compounds the disease ran a course unaffected by treatment Many remedies including large doses of quinine, vaccines etc were tried but proved useless Whatever cures were produced were of a spontaneous nature and these were estimated as high as 25 per cent A concurrent attack of pneumonia or cancrum oris may some times produce a cure Injections of drugs which produce leucocytosis were

The treatment of kala azar is now carried out with two classes of antimony preparations

Trivalent compounds

Patrick Manson originally suggested the use of antimony salts in kala azar and Vianna (1913) was the first to try intravenous injections of tartar emetic, and successfully treated American forms of cutaneous and mucocutaneous leishmaniasis Di Cristina and Caronia (1915) used this salt and successfully treated visceral forms of leishmaniasis in children, prevalent on the shores of the Mediterranean [illegible] r emetic In the same year [illegible] ala azar with this drug and [illegible] l per cent solution but later he found that a 2 per cent solution was quite safe and more convenient Solutions as strong as 5 per cent can be given intravenously but they are apt to produce cough and retching and it is not therefore advisable to use solutions stronger than 2 per cent The solutions may be made in distilled water with or without the addition of 0 85 per cent of sodium chloride It is important to use freshly prepared solutions, as moulds are apt to grow and produce toxins Solutions can however be kept for weeks if 0 25 per cent of carbolic acid is added at the time of preparation

Tartar emetic

Injections were given every second or third day into the veins of the arm the doses being gradually increased from 2 to 5 ccm of a 2 per cent solution keeping a watch whether nausea and gastric symptoms develop Knowles (1920) treated many cases in Assam checking his results by spleen puncture and culture of the material for the presence of *L donovani* The effects were marvellous and after a few injections the fever subsided In some cases rigors followed larger doses, but ceased after a time and the temperature remained at a low level or was normal, the weight of the patient steadily increased and the spleen diminished in size On puncture of the spleen the number of parasites was found to be reduced the blood showed a marked increase in leucocytes

Standard course

The antimonyl tartrates are dangerous if given in doses larger than the patient can bear, the dose should be increased very gradually For an average adult a primary dose of 2 ccm of a 2 per cent solution (0 04 gm of the salt) increased on each occasion by ½ ccm up to a maximum of 5 ccm (0 1 gm) is recommended Subsequently 5 ccm are given on each occasion As a general rule it may be stated that a maximum dose of 60 grains (4 gm) per 100 lbs of body weight is necessary to produce a cure

For debilitated patients the initial dose should be 0 5 ccm increased by 0 5 ccm up to the maximum of 5 ccm For a child of 3 years it is advisable to begin with 0 5 ccm making 2 ccm the maximum single dose For children of 12 the maximum is 3 5 ccm the doses for intermediate ages being in proportion The dose calculated according to pounds of body weight is proportionately larger in children than in adults The injections are given on alternate days throughout the course, they should be given at least twice a week A routine course of [illegible] puncture is then done and 2 or 3 N[illegible] develop and the patient's general co[illegible] he is considered cured, otherwise [illegible] 10 to 15 injections is given and the puncture repeated

The maximum dose can also be modified according to the general improvement in the condition of the patient, the chief factors to be taken into consideration

are fever, the size of the liver and the spleen, and the blood picture. If the body weight has increased, the spleen is redcced to the level of the costal arch or at least by 4 inches, the white cell count is above 6 000 and the temperature is normal by the seventh injection, the full course of 4 gm may be modified to 30 injections (2 88 gm) If the temperature falls to normal by *the tenth injection* 35 injections should be given, and if between the tenth and sixteenth injection 40 injections are necessary If this procedure is followed the cure rate is about 80 per cent

Tolerance is quickly established, and then much larger doses can be given with corresponding beneficial therapeutic effects *In increasing the dosage the* development of tolerance should be judged from the amount of fever, cough and nausea produced These should *not be allowed to be more than slight, in* fact, it may be laid down that nausea is an indication for not increasing the dose The other important considerations are *the state of the pulse, lungs and bowels* and in serious cases of disease where emaciation is marked these should be very carefully examined.

Among kala azar patients the complications usually met with are diarrhœa low blood pressure, broncho pneumonia and sloughing of the connective tissue in the form of cancrum oris Antimony salts if used injudiciously, accentuate all these conditions, and therefore, great caution is necessary in their administration in such cases It is of the utmost importance that when treatment is once started it should not be interrupted Slight diarrhœa œdema of the feet bleeding from the gums, traces of albumin in the urine are not contraindications to treatment, in fact, they demand it Heart failure is the most serious of all the symptoms and cardiac stimulants should be freely used if necessary Intra muscular injections of 0 5 ccm to 1 ccm of adrenalin are useful in counteracting the vasodilator effect and fall in blood pressure

If hæmorrhagic lesions occur give calcium lactate, 10 grains three times a day or *5 to 10* ccm *of a 10 per cent solution of calcium chloride intravenously* If œdema of the feet becomes evident the doses should be regulated with utmost caution The treatment is continued *till the temperature becomes normal* The fever does not as a rule subside before ten injections have been given In a few cases the temperature *may fall after 3 or 4 injections, in others it may* keep above normal till 40 injections have been given A few cases show a slight rise of temperature *after each injection* In some cases fever and *rigors occur* after the first injection This is believed to be due to the destruction of parasites by the compound, *as such reactions do not occur in patients who are not suffer ing* from kala azar, and they become less and less marked as the patients improve.

For the next five years after the introduction of antimonyl tartrates little further progress was made in the treatment of the disease *in India Sodium* salts were substituted for the potassium salts and a number of purified brands of the antimonyl tartrates suitable for intravenous injection were *put on the* market The greater solubility of sodium antimony tartrate makes it possible to prepare a scale form of the salt As *the purity of the salt is essential for the* preparation of the scale form, it gives the practitioner greater security With scale preparations the severe reactions met with *in the early days of treatment* were minimised A larger number of other antimonyl tartrates were prepared but they proved to be no more effective *than the antimonyl tartrates* of sodium and potassium

(1) Pentavalent Compounds

The introduction of these pentavalent compounds of antimony was an important advance in the treatment of kala azar and marked the second phase in the treatment of leishmaniasis with antimonials The advantages claimed for the pentavalent aromatic compounds according to Napier (1927) are —

Advantages

(1) These compounds are much less toxic and can therefore be administered in larger doses The minimum lethal dose is 15—25 mgm per kilo in mice in the case of the trivalent compounds whereas it is 200 to 500 mgm in the case of the pentavalent compounds

(2) The total amount of antimony which is necessary to effect a cure can be administered in a much smaller number of doses About ten doses of the pentavalet compounds against thirty doses of sodium antimony tartrate can be looked upon as the average number necessary for an ordinary case This reduction in the number of injections means a reduction in the time the patient is under treatment from two months to about three weeks which in its turn means that a greater percentage of the dispensary class of patients will complete a full course of treatment

(3) Resistant cases which respond slowly when treated with the tartrates improve rapidly with larger doses of antimony in the form of the less toxic pentavalent compounds On the other hand certain cases which fail to respond to pentavalent compounds have been cured by injections of tartrates

(4) Certain disagreeable symptoms such as coughing and severe joint pains which are frequently associated with the tartrate treatment do not occur when the pentavalent compounds are used In a number of cases these symptoms are so severe that they necessitate the reduction of the dosage to such an extent as to prolong the course of treatment almost indefinitely and reduce considerably the chances of an eventual cure

(5) The death rate amongst kala azar patients under treatment has been very markedly reduced since the introduction of the pentavalent compounds One of the most frequent causes of death during the course of treatment namely pneumonia has been almost entirely eliminated

Napier (1924) reported a death rate of 14 4 per cent in a series of 139 cases treated with sodium and potassium antimony tartrate The same author (1926) found the death rate to be 4 2 per cent in a series of 167 treated in the Carmichael Hospital for Tropical Diseases with six different pentavalent compounds

Disadvantages

The disadvantages of pentavalent compounds are comparatively few The post treatment jaundice is a little more frequently encountered but it is not so serious as is the case with organic arsenicals Anaphylactoid symptoms may suddenly appear towards the end of the course of injections but these are of a mild type *There is only one thing which stands in favour of the antimonyl* tartrates and that is the high cost of the pentavalent compounds Taking 3 gm as the total dose necessary to effect a cure the cost of curing a patient will be a few annas with tartrates against a few rupees in case of the pentalvalent compounds

Dosage

Dosage of pentavalent compounds The initial dose suggested in the case of urea stibamine and allied compounds is 0 05 gm increased by 0 25 gm at each

injection up to 0 2 gm It is better to start with 0 1 gm for the first dose 0 2 for the second and 0 25 for the subsequent injections With stibosan and neostibosan an
Children shoul
doses than adu
children of 6 years 0 15 gm and children of ten years or over 0 2 gm

The pentavalent compounds of antimony have completely revolutionized the treatment of kala azar in India and with neostibosan the toxic effects observed in the case of other preparations, have been reduced to the minimum The standard scheme in adults consists of 10 injections one every other day, the initial dosage given is 0 2 gm followed by 0 3 gm In the case of children relatively larger individual doses are required It was found possible to reduce the duration of treatment by means of the concentrated course (0 2 gm followed by 7 doses of 0 3 gm each per day) to 8 days and by means of the hyper concentrated course (0 3 gm, 0 4 0 5 0 6 gm) even to 5 days The 8 days treatment appears to constitute the optimum and even with this toxic symptoms may appear

If the original course lasting for 3 weeks is given clinical improvement occurs steadily during the course of the treatment The fever comes down usually after the 4th to 5th injection and the volume of the spleen is reduced A characteristic feature is the rapid return of the leucocytes to normal and there may even be leucocytosis, the eosinophiles may show a marked increase the red corpuscles count approaches normal

In the intensive treatment the clinical symptoms are often influenced to a marked degree only at the end of the course the curative process continues as a result of the after effects of the treatment The best guarantee for successful treatment is said to lie in the total dosage administered which is 3 0 gm per 100 lbs of body weight for mass treatment The determination as to whether the cure is permanent or not is furnished by an examination made 6 months later The fact that with the standard treatment a very high percentage of patients can be cured and that intensive treatments or repeated treatments are only rarely necessary is of great importance in combating kala azar in India

The rapid excretion of the major part of the pentavalent preparations of antimony as compared with tartar emetic—subsequent to therapeutic doses shows that no cumulation need be anticipated during the treatment even if this is greatly intensified

Most of the compounds are suppl ed in sealed ampoules contain ng the dose requ red The top of the ampoule is broken off and the contents are poured into a sterile test tube containing 3 ccm of *sterile distilled water not less than 3 ccm should be used for 0 2 gm* of the drug This is sucked up in a sterilised syringe and injected in the usual way If ampoules are not available the drug is weighed on a clean piece of paper The solutions should be prepared at the time of the injection whenever possible but they can be kept for a few hours.

urea can be completely separated from the compound by repeated washing with alco ю
Besides the variation in the composition of different specimens on the market even those prepared by the same firm vary enormously The antimony content shows a variation from 20 to 43 per cent Ureastibamine is a brown amorphous powder soluble in water forming

a clear yellow solution Its toxicity is very low The initial dose is 0 1 gm increased by 0 05 gm up to a maximum of 0 25 gm given twice weekly The patients quickly develop tolerance to the drug and its action in restoring the normal leucocyte count is rapid and most beneficial The average amount of the drug necessary for the cure of a case is 2 6 gm the average number of injections is 10 to 12 and days of treatment 32 as compared with 30 to 90 injections and a total period of nearl three months in the case of antimony tartrates The author has successfully t
injections of urea stibamine for 6 to 8
and subsequent doses 0 55, a total of 2
the individual The duration of treatment has thus been reduced to less than ten days The earlier a case is treated the more effective the treatment

With higher doses hæmorrhages from the gums nose and stomach sometime occur and even retinal hæmorrhages and collapse have been observed The solution of the drug should not be boiled and the solid drug should not be kept exposed to air

Chemically amino stiburia is p aminophenylstibinic acid combined with urea and glucose The addition of glucose is said to add to the stability and to the diffusibility of the drug This compound is quite effective against leishmaniasis The total quantity required to produce a cure was 3 35 gm per 100 lbs that is about the same as other pentavalent aromatic compounds It is useful in resistant cases of kala azar

Stibosan (von Heyden 471)

Von Heyden 471 is chemically metachlor para acetylaminophenylstibiate of sodium It is a light brown powder, non hygroscopic and does not decompose in an ordinary corked bottle at room temperature It is readily soluble in distilled water and forms a sterile solution which does not decompose readily

Stibamine glucoside or Neostam.

Neostam was prepared by Henry of the Wellcome Research Laboratory Napier (1929) treated 57 cases with this drug with good results The compound is easily soluble in distilled water making a 4 per cent solution and is injected intravenously in doses of 0 05 to 0 3 gm An initial dose of 0 1 gm and a maximum dose of 0 2 gm are satisfactory dosage for patients of average weight The injections are given on alternate days The total curative dose is 2 to 3 gm The drug is well tolerated in comparatively large doses

Von Heyden 693 or Neo stibosan

Neo stibosar
of 61 cases wit
mean dose was
to be superior
a complete cure
and has good
less common w
of vomiting

Neostibosan B

Neo stibosan B is of the same composition as the above but prepared differently, it was introduced to avoid vomiting This compound forms an isotonic solution in 25 per cent concentration and can be given effectively intramuscularly but intravenous route is preferable in adults, 0 3 gm can be given by daily
disease
required
the max
considerably after 3 weeks and patients gain weight In some cases progress is slow Any sharp rise of temperature is probably due to latent malaria In relapsing cases the temperature mounts slowly Patients afebrile at the beginning of the treatment commonly show febrile reaction daily or a sharp rise after each injection

Solustibosan

One disadvantage of neo stibosan is that when dissolved in water it does not make a very stable solution This drawback has been overcome by a new pentavalent antimony compound 'solustibosan' It is probably a derivative of
lourless solution
ntent is 20 mgm
ccm of a 5 per

cent solution of neostibosan which contains 21 mgm of antimony It is stated to be less toxic than neostibosan 18 5 ccm per kilo of body weight is lethal dose for a mouse as against 6 ccm of a 5 per cent neostibosan solution The drug may be given subcutaneously intravenously or intramuscularly

Excretion takes place exceptionally quickly On the first day about 80 per cent of the injected Sb appeared in the urine and 1/4 per cent in the faeces After 48 hours only traces are found in the excretions The good general tolerability of solustibosan is thus due to its rapid excretion Repeated large doses of antimony can therefore be given at short intervals without producing cumulative effect With neo-stibosan approximately 50 per cent was found in 24 hours in the urine

The drug is in the same class as neostibosan and can be given intramuscularly

Relative value of pentavalent compounds in the treatment of kala-a ar The works out to be 0 054 and 0 06 gm curative value is about the same entavalent compunds was nearly equal but was lowest with neostibosan Th the fever subsided was as follows —Stibo 5 4 urea stibamine 5 1 neo stibosan (No san and neostibosan are the most stable compounds Neostibosan is the most innocuous and produces a cure in the shortest period it gives the lowest death rate during treatment Patients can now be cured with a routine treatment of eight daily injections of 0 3 gm of neostibosan

The course of the disease under treatment The fever usually subsides after *the fifth injection or even earlier but it may persist for a fortnight or more* In most cases the downward tendency of the temperature is immediately apparent in some cases the temperature remains at about 100°F throughout the course of injections only coming to normal when the course is discontinued In some patients a reactionary rise after each injection is observed A sudden sharp reaction means that the dose has been too big

The general condition of the patient begins to improve soon after the injections are started The weight may decrease slightly at first but then rapidly increases during the course The hair ceases to fall out and regains its normal lustre the appetite improves and there is a sense of well being In women *menstruation usually begins when the course of treatment is ended* The spleen

liver seldom shows any tendency to decrease until after the injections have been completed

The blood picture improves rapidly and by the time the course is completed the leucocyte count is normal or may even indicate leucocytosis there is a noticeable increase in the eosinophiles The erythrocyte count also shows an increase

No dose however large can be guaranteed to produce a 100 per cent cure rate A spleen or liver puncture gives the best indication of cure but it should be remembered that the effect of antimony continues for some time after the

last injection This is shown by the fact that patients who show Leishman donovan bodies on spleen or liver puncture become entirely negative some weeks later The best plan is to give a full course of injections and if there is a relapse a more intensive second course should be started

Relapses

If the full amount of the drug has been given relapses are not very common, they are only frequent after insufficient treatment There is no evidence to show that patients who have had previous injections of antimony require much bigger doses to eradicate the disease in the event of a relapse but the disease in some cases is much more resistant and these require larger doses When a relapse occurs the patient should be given a more prolonged course of treat ment A definite enlargement of the spleen usually accompanies a real relapse as distinguished from other forms of fever In relapses after antimony tartrates one of the pentavalent compounds should be tried

(2) Antimony Resistance

Resistant cases

Kala azar patients are divided into three different categories (*a*) patients who react rapidly the types of leishmania are sensitive to antimony (*b*) patients who react slowly and (*c*) resistant cases due partly to incomplete irregular and interrupted treatment and partly in some instances to a primarily resistant form of leishmania Generally speaking Mediterranean kala azar is more difficult to influence than Indian kala azar and in consequence larger doses should be given The preparation of choice is neostibosan of which a single dose in obstinate cases should be increased to 0 6 gm and the injections made in rapid sequence Unnecessarily long intervals between injections might give rise to antimony resistance in cases of leishmania With intensive dosage no cases of kala azar resistant to neostibosan should occur The aromatic diamidines are indicated with antimony resistant cases of kala azar the cases showing hypersensitive reactions to antimonials and the cases complicated by Pulmonary Tuberculosis Also one of the compounds viz pentamidine isethionate is very suitable for the treatment of the cases in which intravenous injections are different Pentamidine is well tolerated by the intramuscular route in a 10 per cent solution The aromatic diamidines are contraindicated in the cases with Jaundice hæmorrhages ascites or signs of renal failure

Aromatic diamidines

Noma in children

Treatment of Noma complicating kala-azar in children—Noma is a very serious complication of kala azar and neostibosan has been used in its treatment with very successful results in children sometimes in conjunction with blood transfusion and careful local treatment

The total dosage given at first was 1 8 gm whch was subsequently increased to 2 to 2 25 gm depending on the age of the patient the duration of the disease and the condition of the liver and spleen The initial doses were mostly at the rate of 0 1 gm per day administered intravenously increasing to 0 2 gm per day The following basic rules for the treatment of kala azar in children with noma as a complications have been given —

1 Give early large intravenous blood transfusion before neostibosan treatment is started and repeat thereafter when indicated

2 Start with full daily doses immediately following the first transfusion When a total of 1 gm has been given the drug may be discontinued after a few days if the local and general conditions are not progressing satisfactorily

3 Careful local treatment is very helpful in keeping the mouth and wound clean.

4 As a prophylactic measure in the prevention of noma every kala azar patient who has hæmoglobin reading below 50 per cent and very low white cell count, should receive

a large blood transfusion before neostibosan treatment is started and oral hygiene should receive careful attention

Antimony compounds in therapeutic doses have no marked effects on the gravid uterus Treatment therefore should not be withheld in any stage of pregnancy Many pregnant women treated with antimony go on to full term and give birth to healthy children

(3) Evidence of Cure

(a) subsidence of fever and
maint l health and gain in weight
(c) of leucocyte count to near
about the normal level *i e*, *about 5 thousand* per cmm, and (*e*) *well* marked improvement of hæmoglobin value There are really no good criteria for permanent cure of l ala azar A patient may relapse after fulfilling all the criteria of immediate cure and no parasites being found on sternal puncture after treatment The best *criterion of permanent cure that holds good* for 95 per cent of the cases of Indian kala azar is the freedom of the patient from all symptoms of kala azar for a period of six months after immediate clinical cure Relapses after this period are extremely rare It has been shown that even though cultures from the spleen *and liver puncture are positive weeks or months after the completion* of treatment, the patient may still attain a cure During treatment with pentavalent antimony compound the aldehyde and antimony tests become uncertain at first and after the full course of treatment soon become negative

Lloyd and Paul s test In normal serum there is on the average 0.16 gm of euglobulin
5 *per cent of total globulin in well* established
100 ccm *i e* 40 to 50 per cent of the total globulin
ethod of protein graphs to estimate the cure of
compounds The protein fraction estimations are
scribed by Robertson (1924) There is a steady
ady descent of euglobulin and finally euglobulin
attains the normal figure of approximately 0 1 gm per 100 *ccm of serum when there is* complete cure The graphs give an index of the condition of the disease It is suggested that high globulin content of serum in kala azar is an immunity response and such cases react to treatment rapidly while the low protein type of case with a weak aldehyde test *represents the opposite condition*

Chopra and Choudhury s test By noting the time of gelation with formalin of the sera from the blood of kala azar patients it is possible to indicate in a general way the progress towards cure Information regarding progress towards cure may be said to be *satisfactory if the time of gelation is more* than half an hour If however the time of gelation before treatment is known and this can be easily determined from an aldehyde test the corresponding increase of *the time of gel formation also gives useful information*

5. Mode of Action

The mechanism of the curative action of antimony compounds in leishmaniasis and bilharziasis is not understood The important factor in the treatment of all protozoal diseases is that when an attempt is made *to exterminate* these parasites *in the tissues* what appears to take place is that the drug destroys the majority of the parasites The body resistance then rises and the patient s own natural powers of resistance finally eradicate the residual infection *This is* almost certainly the case in kala azar where *not infrequently a* patient at the *conclusion of a course of* treatment may still show a few leishmania in the film on spleen puncture and yet remain in perfect health thereafter and be cured The same appears to hold good for malaria and trypanosomiasis and probably for amœbiasis also

Experimental work

In vitro experiments show that tartar emetic has little action on the cultures of leishmania The toxic effects are not increased by bringing it in contact with fresh animal

[illegible]

pentavalent organic antimony compounds are first reduced to the trivalent state before they become active It is very probable that the antimony ion in some form constitutes the parasiticidal agent but whether oxidation or reduction occurs forming new compounds or whether some protein compounds are formed in the serum is difficult to say The mechanism appears to be very similar to that of the action of mercury on the spirochætes and [illegible]

[illegible]

after the injection With the pentavalent compounds there is an interval of from one to two days before the trypanosomes disappear but whether this latent period is due to a gradual reduction to a trivalent compound is not known In human kala azar there is also an interval which suggests that antimony in some way stimulates certain body functions rendering the body environment detrimental for the development of leishmania

Role of spleen

Chopra and Das Gupta (1927) showed that pentavalent compounds given intravenously stimulate the rhythmic contractions of the spleen which help to release parasites from the heavily infected cells while increased functioning of the adrenals, dialates the vessels of the liver and spleen thereby increasing capillary permeability and diminishing the nutrition of the endothelial cells If the action of antimony was merely stimulatory better results would be obtained by repeated small doses Clinical experience however shows that best results are obtained by pushing the treatment to the point of physiological limits It has been suggested that an important factor in producing a cure is the immunity response of the individual patient

Whatever may be the exact mode of action there is no doubt that the death rate in kala azar has been reduced from 90 per cent to 5 per cent and that in Assam and Bengal on account of extensive use of the antimonials the disease no longer exists in epidemic form and may in time completely disappear

6 Routes of Administration

By the skin

A five to ten per cent ointment of metallic antimony in lanoline base was recommended in the treatment of leishmaniasis one drachm being rubbed over the abdomen every second or third day It has no appreciable effect on the course of the disease Oriental sores have been successfully treated with a 2 per cent ointment of tartar emetic the application being made at night The irritant action of tartar emetic when applied to the skin in the form of an ointment is due to its being broken up by the acid formed by decomposition of the sweat If sodium bicarbonate is added to the ointment the irritating effects are considerably reduced

By mouth and per rectum

The antimony salts are not suited for administration by the mouth except in very minute quantities Their irritant action gives rise to emesis and they are not easily absorbed from the alimentary canal This route cannot be adopted when it is necessary to introduce large amounts into the body as in cases of protozoal diseases

Rectal injections of tartar emet[illegible]

a concentration in the blood lethal for leishmania

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scular

Subcutaneous injections produce cellulitis and abscess formation Urea stibamine and allied compounds (stiburea amino stiburea stiburamine *ureastibol* etc) are administered intravenously in 5 per cent solution in sterile re distilled water Neostibosan is administered intravenously in 5 per cent solution and intramuscularly in 25 per cent solution in sterile re distilled water Sodium antimony gluconate (stibatin solustibatin myostibatin etc) as supplied as a ready made solution containing 20 mgm of antimony per c c and also as solution containing 100 mgm of antimony per c c is best administered intramuscularly although it can be given by the intravenous route also The aromatic diamidines stilbamidine isethionate (M & B 744) and pentamidine isethionate (M & B 800) is administered *intramuscularly* in 10 per cent solution and intravenously in 1 per cent solution in sterile re distilled water

Intramuscular injections even of the double salts are very irritating Not only is severe pain produced but extensive *necrosis of tissues at the site* of injection occurs Attempts have been made to discover preparations which can be given this way without harmful effects Such compounds as antimosan fouadin stibosan and neostibosan administered by the intramuscular route are non irritant and quite effective, stibosan and solustibosan are drugs of choice for this The advantages of this route are that as compared with the intravenous route little skill is required Besides in very young children it is sometimes impossible to get at the veins embedded in the subcutaneous tissue

By intravenous method *uniform success can be claimed and most of the* antimony [illegible] the blood stream with safety *The only* [illegible] ly attained [illegible] er of this route is sligh [illegible] on of dosage of these compounds The technique of intravenous injection is described in the chapter on intravenous therapy

7 Toxic Effects

A *Toxic reactions produced by antimony tartrate injections*

Certain toxic symptoms follow injection of antimonyl tartrates Of all the *symptoms cough metallic taste* and a feeling of tightness in the chest are most *frequent Cough retching and colic indicate a need for caution* Jaundice, and a larger amount of albumin in the urine than can be accounted for by the disease are signs of danger So far as is known acute toxic reactions of the 'nitritoid crisis type do not occur with antimonyl tartrates The frequency of toxic symptoms depends partly on the sensitivity of the patient and also on the severity of the disease and length of treatment The toxic symptoms if alarming or persistant may call for reduction of dose If there is persistant quick pulse severe epigastric pain persistant vomiting or reduction in the amount of urine the course should be suspended Nephritis and *jaundice are a contra indication to injections* A marked rise of temperature enlarged and tender lymphatic glands diarrhoea and *necrosis of gums are danger signals* The toxic symptoms that are produced may be grouped as follows —

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Severe spasmodic coughing may occur immediately after the injection and may be so severe as to end in vomiting It is an indication that the dose has been excessive and should not be increased After a large dose the patient *may vomit 5 or 6 times* By decreasing the dose and then gradually increasing it a certain degree of tolerance can be established Both coughing and vomiting may be induced by giving the injection on a

full stomach or by giving it rap dly Metallic taste lack of appetite a vague d scomfort in the abdomen sometime increasing to a convulsive pain and finally diarrhoea my occur vom ting may be severe and alarm ng Headache dizziness and fever may be present

chest and sat on in During

Cardiac symptoms

Changes in electrocardiogram may appear in some cases during antimony treatment The S T interval as well as the T deflect on have been found to alter The extent of the electrocardiographic changes may be parallel to the degree of chronic bradycardia. The characterist cs from the irdiographic abnormalities from intoxicat on of the e occured several hours

These are said to occur more commonly during treatment of trypanosomiasis Loss of consciousness with incontinence of ur ne and fæces may sometimes ensue Severe headache or hemicrania has been observed after 6 to 9 injections and it does not clear up till the injections are d scont nued Herpes zoster may occur

Cerebral symptoms

Severe joint and muscular pains frequently occur but are less common towards the end of the course Pa n in one or both shoulders and lumbago are common complications The wrist joint knee joint and ankle joint may be affected and the pain may last for some time Usually the joint pains commence 4 to 6 hours after an injection generally after a total of about 10 grams of antimony tartrate and they last for about 12 hours Ten grains of aspirin given half an hour before the pains are expected to begin dimin sh the r severity Codeine in 1/6 to 1/4 grain doses counteract most of these symptoms

Arthritic symptoms

i may occur on any part of the body Urticaria arely observed Classic symptoms of antimony and cachexia may develop A sharp rise of injection of faulty solution Profuse sweating or fainting is of rare occurrence

Other symptoms

Fouad n wh ch is also a trivalent preparation unlike ant monyl tartrates has no local irritant action and can be given intramuscularly the shock due to intravenous injection is thus avoided The general symptoms above described may be absent or much reduced in intensity and frequency There is less injury to the liver and kidneys

B Complications after injections of penta 'alent compounds

There is complete absence of asthmatic symptoms peculiar to trivalent compounds were obse of antimo pounds Nausea and vomiting are seen in about 10 per cent of cases but rarely with neostibosan (von Heyden 693 B) except when the dose is very large If nausea and vomiting persist the dose should be reduced The tendency to vomiting can often be overcome if the dose is increased very gradually After injections of stibosan vomiting not infrequently occurs Generally the vomiting begins within 20 minutes of the injection and it may be preceded by giddiness If the patient remains quiet in bed vomiting may be avoided The injections should not be given immediately after a meal Diarrhœa may occasionally occur

Nausea and vom ting

towards the end of the course and may be severe The motions are dark watery and frequent they contain no blood or mucus Fatal collapse and death are on record A severe attack of shivering lasting for 2 hours may be the only feature Cardiac cerebral and arthritic symptoms have not been noticed

Symptoms of an anaphylactoid nature resembling the 'nitritoid crisis (occurring with organic arsenicals) sometimes develop This is to be expected as both these series of compounds are of semi colloidal nature and give rise to changes in the blood They also produce an enormous rise of pulmonary pressure These symptoms set in suddenly after the sixth or seventh injection when the patient has been receiving maximum doses Within a few minutes of injection the face becomes puffy the voice husky there may be an urticarial rash on the body dyspnœa and stertorous breathing The patient has a feeling of impending death The pulse becomes weak and imperceptible, the patient is cyanosed and coma and collapse may soon supervene The condition though alarming is rarely fatal, and as a rule all symptoms disappear in two hours The puffiness of the face may last for as long as 24 hours These symptoms are more frequently observed with amino stiburea and urea stibamine and are rare with neostibosan Injections of a few minims of adrenalin or pituitrin relieve the symptoms If these symptoms occur it is best to abandon treatment with a particular compound recommencing it with minute doses of some other compound Nausea and vomiting are frequent if the injection is given soon after a meal, consequently the injection are best given two hours or so after the patient has had a cup of milk

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capillaries of the lungs and other organs Chopra and his associates ([illegible]27) *have shown that when organic antimony compounds come in contact with the* serum of kala azar patients a thick flocculent precipitate is formed This *precipitate is not produced* with non kala azar serum and this reaction has been used as a diagnostic test for the disease It is possible that some of the untoward symptoms produced may be due to this precipitation

Rarely acute congestion of liver or even symptoms of acute hepatitis are produced by injection of these compounds *The liver becomes enlarged tender* and painful [illegible] rises and there may be jaundice The symptoms disappear if
of the compo
after the cou

The chief factors to be taken into account in the selection of a compound are the toxic effects produced the time necessary to produce a cure *the ease of* administration and the relapse rate after treatment Anaphylactic symptoms are common with urea stibamine and aminostiburea *but are rare with stibosan and* neostibosan The relapse rate is also lower with the latter compounds and they are more stable *Neostibosan is the easiest to administer as it can be given* intramuscularly in doses of 0 1 gm to 0 3 gm without causing pain and it is effective Both these *compounds are however expensive* Urea stibamine and *allied compounds are nearly* as effective and are slightly cheaper

The human body can stand large doses of antimony especially when it is *given intravenously* The reason for this is that when administered by this route quantities are eliminated from the system by the kidneys

Antimony salts should be employed with great caution in weak, anæmic and emaciated subjects If disease of the heart kidneys or lungs co exists special care should be taken Before starting the injection and during the course of treatment the urine should be examined frequently for the presence of albumin

injection are followed by thrombosis of the vein employed Intramuscular injection of stilbamidine is very painful but pentamidine is well tolerated by the intramuscular route No immediate reaction are caused by the intramuscular injections of aromatic diamidines

8 Summary

The treatment of Kala azar with antimony compounds is briefly as follows —

Trivalent compounds

Sodium antimonyl tartrate is the drug of choice and is given intravenously in two percent solution in normal saline every other day The first dose is 2 ccm then 3 ccm 4 ccm and 5 ccm the last being the maximum dose At least twenty five injections are required This compound is less effective than pentavalent compounds and is liable to produce reactions and relapses are frequent

Pentavalent Compounds

Neostibosan and Solustibosan are the drugs of choice but in India urea stibamine is largely used These drugs are used in 5 per cent solution intra venously and 25 per cent solution for intramuscular administration (only Neostibosan and Solustibosan) in double distilled pyrogen free water

The initial dose in adults is 0 2 gm increased to 0 3 gm for subsequent injections which are given daily Usually eight to twelve injections are required Children get small doses but a child over sixty pounds in weight gets the adult dose Anaphylactoid reactions (nausea vomiting urticaria dyspnoea) if they occur should be controlled with five to ten minims of adrenalin given intra muscularly Anaphylactoid reactions are common with urea stibamine if a course has already been taken with this drug, in such cases the intial doses must be small

9. Aromatic Diamidines

It was shown in *1937* that diamidines possessed marked trypanocidal activity This opened up a new field of biological and chemical research In 1942 the preparation and comparative trypanocidal activity of numerous aromatic diamidines was described The 4 4—diamidino derivatives of diphenyl ether stilbene diphenoxy propane and pentane were later tried in Leishmaniasis and Trypanosomiasis *The chemical constitution of these compounds may be shown* as follows —

Phenamidine	—	Am R O R Am (4 4 diamidino diphenyl ether)
Stilbamidine	—	Am R Ch Ch R Am (4 4—diamidino stilbene)
Propamidine	—	Am R O $(CH_2)_3$ O R Am (4 4—diamidino 1 3 diphenoxy propane)
Pentamidine	—	Am R O $(CH_2)_5$ O R Am (4 4 diamidino 1 5 diphenoxy pentane)

Where Am stands for the amidine group NH_2 C (NH) and R stands for C_6H_4.

The position of substituent amidine group in the benzene nucleus is in each case 4.4

Pharmacological Action—All the four compounds have depressant action on the circulatory system There is a marked transient fall in blood pressure. The fall of blood pressure is much reduced or prevented by a previous injection of calcium and could mainly be accounted for by peripheral vasodilatory effect of these compounds. The depressant action of these compounds is only partially antagonized by atropine The effect of the diamidines on the heart is small and transitory In general low concentrations stimulated and high concentrations depressed the heart There is however no marked deleterious effect The pressor action of adrenaline is very much reduced by the diamidines

Following slight initial stimulation the respiration is greatly depressed in intact animals accompanied by dyspnoea which may be due to spasm of the bronchi On intravenous administration to anaesthetized animals the main effects observed are increase in depth and volume of respiration Recovery takes place as soon as blood pressure regains its normal level

All the drugs stimulate the plain muscles such as that of intestine and uterus in high concentrations These effects were not abolished by atropine The diamidines have an ergotoxine like action and reduced the action of adrenaline on the uterus and on perfused vessels of rabbit's ear and cat's hind limb

All the four compounds have the same toxicity The diphenyl ether compound (phenamidine) is less toxic than the stilbene derivative while the diphenoxy compounds are slightly more toxic

The administration of the lethal doses depresses the respiration greatly which ultimately becomes very difficult and violent efforts are made till ultimately the animals lie prostrate and die after a few convulsions The chronic toxicity experiments also show that there is cumulative toxic reaction

These compounds have during recent years been tried in the treatment of human sleeping sickness and visceral leishmaniasis While these clinical trials are still in progress in different countries encouraging results in these two diseases have been reported by many workers

Treatment with aromatic diamidines is a definite advance and in Sudan and in Calcutta better results have been obtained than formerly with antimony In antimony resistant cases the results have been very striking

and

Napier has pointed out that these drugs should be used with great care and should preferably be given in antimony resistant cases Two compounds Stilbamidine isethionate (M & B 744) and pentamidine isethionate (M & B 800) have been tried The drugs occur as white powder and are marketed in sealed ampoules The powder is dissolved in distilled water to make a 1 per cent solution for intravenous and 10 per cent solution for intramuscular injection the injections should be given slowly the maximum dose of stilbamidine for adults children and infants being 3 mgm (0 003 gm) per kilo body weight ¼ ½ and ¾ of the maximum dose for the first second and third injections For intramuscular injection maximum dose may be given from the beginning of the course of injections Maximum dose of pentamidine isethionate is 3 to 4 mgm per kilo for all age groups for intravenous injection maximum dose is reached in two to three stages as with stilbamidine and for intramuscular injection maximum dose may be given from the beginning of the course of injections The adult dose is 0 025 gm as initial dose, if this gives a reaction next day the dose given is 0 035 gm but it is preceeded by an injection of 0 25 ccm of 1 in 1 000 adrenaline If the reaction is mild the next dose of 0 05 gm is given without adrenaline The doses are increased rapidly by 0 01 gm or 0 02 gm according to reaction produced till a maximum dose of 0 003 gm per kilo body weight is reached Adrenaline is given for the next dose whenever there is a marked reaction to the previous dose and the dose may also be reduced

In Sudan a much more extended course and a much larger do given—0 75 gm in 24 doses or to 4 4 gm in 70 doses The good eff nent is not immediately apparent and the fever may not disappear in t of cases till after the course is completed exacerbation of symptoms n occur after the first few doses

The *mild* reactions are headache flushing of the face sweati burning sensation all over the body In more severe cases headache is and there is giddiness faintness palpitation epigastric pain and vomiting and unconsciousness loss of corneal reflex and incontinance of urine a may occur

Most of these symptoms can be reduced to minimum by giving dose of adrenaline previously and even a moderate dose after the ir will rapidly relieve the symptoms considerably Vomiting is prevented by he drug on an empty stomach but it is preferable to give it two hours after

Subjective disturbances of sensation over the trigeminal nerve h aesthesia paraesthesia anaesthesia formication and loss of sense to light t but preservation of pressure sensation may occur Aneurine in large has been prescribed and relief has followed after injections of cobra ve (0 1 to 1 0 ccm of 1 in 100 000 every third day)

Summary

The aromatic diamidines are very effective in the treatment of Kala a and should be tried in all cases resistant to treatment with antimony compoun These compounds are however very toxic and should be used with great ca The drug of choice is 4 4 diamido stilbene known as stilbamidine which is give intravenously in freshly prepared 1 0 per cent solution in double distilled pyroger •free water no dose should exceed one mgm per pound of body weight Th initial dose irrespective of weight is 0 025 gm increased by 0 01 or 0 02 gm to an individual dose of 0 001 gm (1 mgm) per pound body weight A minimum of ten injections totaling 0 75 gm for a person of average weight (100 lbs) are required The course should not be repeated for at least one month

Post Kala azar dermal leishmaniasis does not respond so well to these compounds as to the antimonials

General Treatment

Complicating infections such as hookworm malaria etc should be treated The blood soon returns to normal after the specific treatment but a course of ron either ferrous sulphate 9 grains daily or Citrate of ammonium and iron 20 › 30 grains daily is decidedly helpful Diet should be light as there is a tendency to diarrhoea on full diet Most patients have good appetite but at the height of fever high protein diet is not desirable

Complications should be treated as they arise Pneumonia is not uncommon If cancrum oris occurs the mouth should be kept clean with eusol solution or hydrogen peroxide or boric lotion It is inadvisable to use strong antiseptics

10 Treatment of Resistant Cases

Napier defines a resistant case as one who has not been cured by an ordinary course of treatment which cures 90 to 95 per cent of cases or there is rel such cases there is still evidence of visceral infection Arom

(x) *General anasarca* In the vast majority of cases the œdema is due to lowering of the colloid osmotic pressure of the *plasma caused by the alterations in the* blood protein viz., hypo albuminaemia and hyperglobulinaemia seen in kala azar The treatment consists essentially of putting the patient to bed, restricting *the fluid intake, the diet should include* protein hydrolysates and specific treatment for kala azar are followed

12. Treatment of Post-Kala-azar Dermal Leishmaniasis

According to Napier diamino-stilbene is not of much value in this condition the only specific treatment being with antimony compounds, though cure is affected with difficulty He has obtained satisfactory results with pentavalent compounds and has used the trivalent compounds such as antimosan and fouadin in some cases with good results He recommends the ordinary course used in visceral infection, but injections should be given on alternate days or even more widely spaced One course is usually sufficient and nodular lesions show signs of improvement, but the hypo pigmented lesions remain unchanged regaining their pigment in the course of a month or so The shrinking of nodules continues for sometime and at least two months should be allowed to elapse before a second course is given

Injection of a 2 per cent solution of berberine sulphate make the nodules shrink, but this is not considered to be a practical method when lesions are *extensive Large doses of potassium when pushed to its physiological limit* may be of value, the nodules may undergo ulceration but heal rapidly after the *drug is discontinued*

Treatment of Kala azar

Summary

Two per cent solutions of potassium or sodium antimony tartrate are used and *injections are given every second* or third day For an average adult 2 ccm of the solution (0 04 gm of the salt) is the first dose, *on* each subsequent occasion the dose is increased by 1 0 ccm till a maximum dose of 5 ccm is attained Afterwards 5 ccm are given on each occasion Generally sixty grains *(4 0 gm) of the salt is required per 100 lbs body weight to affect a cure* For debilitated patients, the initial dose should be 0 5 ccm increased by 0 5 ccm up to a maximum of 5 ccm For a child of 3 years it is advisable to begin with 0 5 ccm making 2 ccm as the maximum single dose For children of 12 years the maximum dose is 3 5 ccm, the doses for intermediate ages are in proportion The injections are usually given on alternate days or at least twice a week thoughout the course and a routine course of 30 injections is given A spleen or sternal puncture is then made for culture, if no flagellates develop and patient s general condition is good he is considered cured otherwise a further course of 10 to 15 injections is given

These compounds have practically *entirely replaced* the trivalent compounds in the treatment of Kala azar in India Neostiban B and urea stibamine are drugs of choice The *standard scheme in adults* consists of 10 injections one every other day The initial dose is 0 2 gm followed by 0 3 gm In case *of children relatively larger individual* doses are required A total dose of 3 0 gm per 100 lbs body weight of the pentavalent compounds is required *to produce a cure*

It is found possible to reduce the duration of treatment to eight to ten days by means of a concentrated course—0 2 gm initial *dose followed by seven doses*

of 0 3 gm each per day Some workers give a hyper concentrated course lasting five days—0 3 gm 0 4 0 5 0 6 0 6 gm—injections being given daily

Eight days' course is, however, the optimum and even with this toxic symptoms appear

If the original course lasting for three weeks is given clinical improvement occurs steadily, the fever coming down after the 4th or 5th injection, the spleen decreasing in size and blood improving In the intensive course, the clinical symptoms are not often influenced till the end of the course, the curative processes continue The criterion of cure is the negative culture for leishmania

Aromatic diamidines

The Amomatic diamidines are toxic and should be used with care and preferably in antimony resistant cases Stilbene is given in doses of 1 mgm per pound body weight, the adult dose is 0 025 gm as initial dose If this gives a reaction next day the dose given is 0 035 gm but it is proceeded by an injection of 0 25 ccm of 1 in 1 000 adrenaline solution If the reaction is mild the next dose is 0 05 gm without adrenaline The doses are increased rapidly by 0 01 gm or 0 02 gm according to reaction produced till a maximum dose of 0 001 to 0 01 gm per pound body weight is reached Adrenaline is given for the next dose whenever there is a marked reaction Ten injections are usually given a total dose of 0 7 gm per kilo body weight and 1 0 gm for resistant cases Toxic reactions are common

Penicillin has been tried in Kala azar but has proved a complete failure

The above courses—laid down are for Indian patients In Sudan China and other places a more intensive course is necessary

CUTANEOUS LEISHMANIASIS

ORIENTAL SORE—MUCO CUTANEOUS (SOUTH AMERICAN LEISHMANIASIS) LEISHMANIAL DYSENTERY

1. Cutaneous Leishmaniasis or Oriental Sore

This is cutaneous infection with *Leishmania tropica* and is known by various names *e g* Lahore sore Delhi boil Baghdad sore etc The lesions (which may be single but are often multiple) occur on exposed parts of the body, infection being conveyed by the sandfly

Epidemiology

Oriental sore is widely distributed throughout the world *i e* Europe North Africa South America Asia Minor Syria Palestine Arabia Persia etc In India it occurs in the dry portions of the Indo Gangetic plain, the Punjab North West Frontier Province Baluchistan and West coast of the Peninsula *P argentipes* the transmitter of kala azar breeds in moist areas and *P papatassi* and *P sergenti* the transmitter of oriental sore is the sandfly of the dry regions The disease is endemic in certain cases but may assume an epidemic form, such an epidemic occurred on the outskirts of Delhi in 1939-40 when 15 to 20 thousand people were affected In the North West Frontier Province and in the Punjab cases begin to appear in June and July and the incidence is highest in August and September In Quetta the maximum infection occurs in September and October All races and ages are susceptible

Oriental sore and Kala azar both occur as a natural disease in dogs and the parasite found—*L canis* is serologically the same as *L donovani*

Aetiology

The mechanism of transmission is similar to that of kala azar *P papatassi* and *P sergenti* become infected by feeding on the indurated edges of the sore and ingest *L tropica* the development of the flagellate takes place in the gut and the organism moves forward towards its mouth the infection is then conveyed to the new host by bite Infection may

occur by direct inoculation from the sore but this is not the usual mode of transmission. A non human reservoir of *infection is suggested* and lizards are suspected In Aleppo and Tehran, dogs are heavily infected and probably act as reservoir

That there is some immunity is shown by the fact that in endemic areas adults are not affected and only emigrants and *children get the sore After natural* infection in man immunity is said to be lasting Auto inoculation is quite common so that immunity cannot be complete especially against hetrologous strains. *Oriental sores do not confer immunity* against other leishmania infections and vice versa.

The presence of the parasite produces infiltration of the layers of the dermis by macrophage cells many of which contain parasites this extends to the subcutaneous tissues *giant cells are sometimes present.* The parasites get into the endothelial cells of the capillaries which become swollen, the blood channels thus become blocked and necrosis results *Cellular proliferation interferes with* the blood supply of the epidermis which is easily damaged by trauma Pyogenic organism gain entry and ulceration occurs, the leishmania organisms are *destroyed when this occurs and are* difficult to find The margins of the ulcer show thickening of the epidermis and finally the granuloma formed is invaded and superseded by fibrous tissue, *when the septic process resolves* the ulcer heals leaving a scar Leishmania as a rule do not occur in the peripheral blood stream

ology

The incubation period may vary from a few weeks to many months, in the majority of cases it is at least three months There is a small itching red pappule surrounded by a pink area at the site of inoculation This increases in size from 1 to 3 cm in diameter and a crust is formed with dry whitish or dark red scales This breaks down in the centre forming an ulcer with clean-cut edges with a sloughing and later a granulating base, surrounded by an area of red induration. If no treatment is given the sore usually heals after a year or so In neglected cases ulceration extends in size and depth and becomes secondarily infected Much disfigurement may result if the sore is on the face.

In some cases, a cauliflower like growth may be formed which may involve a large area *There are also non ulcerating forms which may take the shape of a fleshy* nodule or keloid or lupoid forms

The sore can be easily diagnosed by examination of the lesion for leishmania. In early lesions the organism is easily found but in old ones especially where there is infection with secondary organisms it is often not possible to demonstrate *leishmania In such* cases the sore is cleaned with alcohol and washed with saline the spreading edge is then punctured so that it bleeds the first *blood is wiped with a sterile swab and a smear* is made from the serous fluid which oozes or a culture may be made in N N N medium

The sore should be differentiated from tropical sore Yaws Veld sore etc

In old days the treatment was mainly *local* the ulcer was scraped *with a* Volkmann spoon under an anaesthetic till all friable tissue was removed from the edges and the base and pure phenol was applied The wound was then *aseptically dressed* and it healed up leaving a bad scar This procedure is rather drastic and is not used now a days

Local application of 2 to 4 per [illegible] has been suggested but is very painful powdered pot[illegible] or mercuric chloride methylene blue ointment [illegible]hoxide snow (applied for 5 to 30 seconds and repeated every [illegible] e *been tried* When x rays are available their application is said to cure the ulcer in 10 days

Treatment by ionisation is believed to be effective. The ulcer is cleaned and then covered with a pad consisting of many layers of lint soaked *in 2 per cent* zinc solution This is firmly applied with a bandage and then connected with positive pole of a battery and a current of 36 to 38 volts is passed The application *is continued for* 20 *minutes*, the pad being kept moist. Diathermy has also been tried but not with much success

Local injections of emetine hydrochloride 2 to 5 per cent *solution have* [illegible] the thickened edges and bases of the ulcers,

about 20 minims of the solution is injected at a time and several punctures being made Mepacrine hydrochloride solution have also been used in the same way

The best results have been obtained with berberine sulphate and Napier recommends the following technique —

"If the ulcer is septic, hot magnesium sulphate fomentations and frequent dressings should be used for a few days to make the wound as clean as possible. A 2 per cent solution of berberine sulphate is used, this is injected by means of a tuberculin syringe into the indurated area surrounding the ulcer, about six injections will be required for each ulcer in order to infiltrate the whole circumference of the ulcer, but 1 ccm of solution will usually be sufficient for an average-sized ulcer There will usually be some inflammatory reaction, which should be allowed to subside before further injections are given, it will usually be possible to give the injections once a week From three to six treatments will effect a cure If there are multiple sores, not more than two or at the most three should be treated at one sitting' but treatments can be given daily, the ulcers being taken in turn This treatment, however, cannot be recommended when there are more than half a dozen ulcers"

General treatment, such as intravenous injections of tartar emetic in the same way as in the treatment of Kala azar have been used when the ulcers are multiple Pentavalent compounds (neostibosan), although they cured the ulcer, did not give such good results as trivalent compounds

Fouadin starting with 1 5 ccm and increasing to 5 ccm intramuscularly on alternate days till 8 to 10 injections are given to produce healing

Napier found aromatic diamidines useless

Summary

According to Napier 'in those cases in which there are single or only a few early sores and non ulcerating lesions, beberine sulphate is recommended, in cases with numerous small or moderate sized lesions fouadin or neostibosan [illegible] with extensive ulcers heavily infected [illegible] be had to surgical treatment Until [illegible]de powder should be included in all [illegible] of surgical treatment with antimony [illegible] cases with very numerous extensive ulcers'

Under proper treatment the sore heals up in 2 to 3 weeks

2. Muco-Cutaneous (South American Leishmaniasis)

This is also known as espundia and is a specific condition of the skin produced by *L. braziliensis* and transmitted by phlebotomus The disease occurs in Mexico and many parts of South America

Pathology

The parasite is readily found in the cutaneous lesions in the early stages but with difficulty later they may be found in intact mucous membrane There is no essential difference between cutaneous lesions in this condition and those which occur in oriental sore In infection of the mucous membrane which occurs in 10 to 20 per cent of cases there is œdema of the submucosa and perivascular lymphatic infiltration in which lymphocytes predominate endothelial cells containing leishmania are present. In the second phase the mucosa is swollen and there is disquamation of the epithelium over the infected focus, and superficial necrosis covered by fibrinous exudate. Ulceration and necrosis in the nose mouth and pharynx may result in extensive and distressing lesions which may lead to profound cachexia

In the primary phase there is cutaneous ulceration, and in the secondary phase, there is infection of the mucosa of the buccal cavity and upper respiratory tract. The incubation period is generally 2 to 3 months. The lesions are ulcerating and non-ulcerating and the latter may be *papillomatous or cauliflower like or atrophic, looking like* a red plaque with raised edges. The ulcerating type starts as an itching papule which goes on to pustule formation and eventually an ulcer is formed which may be 9 to 10 cm in diameter. The ulcers are round in shape, have undermined edges and a purulent exudate. The papillomatous type begins in the same way and also exudes serous fluid.

The mucosal lesions take 6 to 18 months to develop and the nasal lesions take much longer. The ulcers start as œdematous swellings which break down giving rise to small granular ulcers which may destroy the whole of the mucous membrane of the nose. They do not affect the tongue or the bones.

This is made easily in the early stages by pricking the edge of the ulcer and making a smear from the exudate. In case of mucous membrane leishmania may be found by making a smear from the exudate obtained by scratching the intact surface. Montenegro's intradermal test is specific. One ccm of a suspension of a culture of *L. braziliensis* in 0.4 per cent phenol is injected intradermally. There is a sharp local reaction in 48 hours, which persists up to 72 hours. The test becomes positive after about a month and remains so throughout the course of the disease.

The disease has to be differentiated from Yaws, leprosy, syphilis and blastomycosis.

Prevention can only be carried out by protection from sandfly bites. A thorough treatment of cutaneous lesions will prevent serious mucosal lesions.

Local treatment is the same as in case of oriental sore. For mucosal lesions antimony has been the mainstay. Tartar emetic has been tried by the intravenous route and fouadin has been successful, the latter is given intramuscularly in 6.3 per cent isotonic solution in doses of 1.5 ccm increased to 5.0 ccm, injections are at first given daily and then on alternate days till 15 to 30 are given. Yatren given intravenously along with fouadin is said to accelerate healing of mucosal lesions. Arsphenamine compounds cure cutaneous lesions but have no effect on the mucosal lesions. Atebrine injected locally and by the mouth is said to be specific for cutaneous lesions.

For mucosal lesions a gargle with sodium bicarbonate solution and wash with 0.1 per cent *solution of tartar emetic is recommended*. *After anaesthetising* with a 1.0 per cent cocaine solution with 1 per cent phenol application of a 2 per cent tartar emetic is said to be effective.

3 Leishmanial Dysentery

In generalised infection with *L. Donovani* ulceration of small and large intestines is commonly seen as a terminal complication. In infantile kala azar in Sicily entero colitis with circular ulcers in the large intestine are a common occurance. The jejunum is thickened without ulceration and columnar epithelium *of the villi disappears.* L. D. bodies can be demonstrated in scanty numbers in the sub mucous coat and in the base of the villi. In the centre of the villi they multiply rapidly and are present in the endothelial cells in large numbers. Bodies resembling L. D. bodies are found in the stools of K. A. patients in whom dysentery like symptoms have been induced with croton oil. These fin[illegible] been *employed as an argument in favour of faecal transmission* of K[illegible] d infection has actually been produced in hamsters from stools of K[illegible]

CHAPTER IV

MALARIA

GENERAL CONSIDERATIONS GEOGRAPHICAL DISTRIBUTION MALARIA PROBLEM IN INDIA AETIOLOGICAL CONSIDERATIONS MALARIAL PARASITES AND VECTORS EPIDEMIOLOGY ENDEMIC INDICES PATHOLOGY OF MALARIA CLINICAL ASPECTS ACUTE PYREXIAL ATTACK SYMPTOMS IN DETAIL DIAGNOSIS OF MALARIA IMMUNITY IN MALARIA MODE OF PRODUCTION—CHEMOTHERAPY OF MALARIA STUDY OF ACTION OF ANTIMALARIAL DRUGS TEST IN BIRD MALARIA TEST IN MONKEY MALARIA THERAPEUTIC TESTS STUDY OF CURES NATURAL CURE ARTIFICIAL CURES EFFECTIVENESS OF ARTIFICIAL CURES COMPLETE CURES—THE CINCHONA DERIVATIVES TOTAL ALKALOIDS TOTAQUINA ALKALOIDS OF CINCHONA THERAPEUTIC EFFICACY QUININE SUPPLY OF INDIA—PHARMACOLOGICAL ACTION OF CINCHONA ALKALOIDS ACTION IN MAN—THERAPEUTICS OF CINCHONA ALKALOIDS QUININE IN MALARIA SYNERGIST OF QUININE DOSAGE CAUSES OF FAILURE OF QUININE THERAPY RELAPSES ROUTES OF ADMINISTRATION OTHER CINCHONA ALKALOIDS IN MALARIA QUININE IN OTHER CONDITIONS—TOXIC EFFECTS QUININE IDIOSYNCRACY CINCHONISM VISCERAL DEGENERATION TREATMENT OF CINCHONISM—MODE OF ACTION OF QUININE SUMMARY F TREATMENT OF MALARIA WITH CINCHONA ALKALOIDS—PREPARATIONS OF CINCHONA ALKALOIDS & ITS DERIVATIVES—PLASMOQUINE PHARMACOLOGICAL ACTION EFFECTIVENESS AGAINST MALARIA—MAPACRINE (ATEBRIN) PHARMACOLOGY EFFECTIVNESS AGAINST MALARIA TOXIC EFFECTS—OTHER DRUGS USED IN MALARIA—THE NEW ANTIMALARIAL DRUGS PALUDRINE EXPERIMENNTAL WORK BIOLOGICAL RESULTS PHARMACOLOGY & TOXICITY PALUDRINE IN HUMAN MALARIA CHLOROQUINE (S N 7618) METACHLORIDINE (S N 11 137) PENTAQUINE SUMMARY OF TREATMENT OF MALARIA WITH PALUDRINE—SUMMARY OF TREATMENT OF CLINICAL MALARIA—PROPHYLAXIS OF MALARIA GENERAL MEASURES CHEMO THERAPEUTIC SUPPRESSION PREVENTION AND CONTROL OF MALARIA IN WORLD WAR II—SPECIAL FORMS OF MALARIA CHRONIC MALARIA MALARIA IN CHILDREN—BLACK WATER FEVER GENERAL TREATMENT—INDUCED MALARIA GENERAL TREATMENT—ANTIMALARIAL DRUGS IN SIMIAN MALARIA—PRESENT POSITION OF ANTIMALARIAL DRUG THERAPY CINCHONA ALKALOIDS SYNTHETIC ANTIMALARIAL DRUGS THE AMINO-QUINOLINE DERIVATIVES (PLASMOCHIN PENTAQUINE CHLOROQUINE) ATEBRINE AND SIMILAR COMPOUNDS SULPHONAMIDES THE I C I SERIES (PALUDRINE) CINCHONA ALKALOIDS VERSUS SYNTHETIC ANTI MALARIAL DRUGS

1 General Considerations

Introdu

The periodic attacks of fever coming on with shivering and passing off with sweating have been recognised as a clinical entity for many hundred years In the *Charaks Samhita* there are references to fevers spread by mosquitoes and it has been suggested that these refer to malarial fevers Such fevers were also known at the time of Homer The term malaria however was employed for the first time for this disease by Italians under the impression that the fever was due to miasmatic exhalations from marshy grounds (mal bad aria air) Many other names have been given to this disease from time to time some of these names such as marsh fever tropical fever coastal fever and acclimatization fever were indicative of the supposed origin of the disease while others such as ague and febris intermittens had their origin in the chief characters of the disease Hippocrates definitely established the entity of the disease and further divided the intermittent fevers into three main groups quotidian tertian and quartan

Synony

Definit

Malaria by present day usage is not defined on a clinical but on a parasitological basis *i e* the term means infection by one of the malarial parasites (Christophers) It is characterized by fever anæmia enlargement of spleen and sometime fatal complications

The Par

The malarial parasites belong to the class *Sporozoa* ... *morpha* ... es of ... *rum* ... *s*

In the primary phase, there is cutaneous ulceration and in the secondary phase there is infection of the mucosa of the buccal cavity and upper respiratory tract The incubation period is generally 2 to 3 months The lesions are ulcerating and non ulcerating and the latter may be papillomatous or cauliflower like or atrophic, looking like a red plaque with raised edges. The ulcerating type starts as an itching papule which goes on to pustule formation and eventually an ulcer is formed which may be 9 to 10 cm in diameter The ulcers are round in shape have undermined edges and a purulent exudate. The papillomatous type begins in the same way and also exudes serous fluid

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The malarial parasites belong to the class *Sporozoa* Sub-class *Coccidiomorpha* order *Haemosporidiidea* and genus *Plasmodium* A number of species of Plasmodia are recognized the better known ones being *P vivax* *P falciparum* *P malariae* and *P ovale* infecting man *P knowlesi* and *P inui* infecting monkeys and *P relictum* *P gallinaceum* and *P lophurae*, infecting sparrows chicks and

ducks respectively Plamodia are amœboid organisms which inhabit the tissues and erythrocytes of the vertebrate hosts (man monkeys, birds cattle etc.) and produce a characteristic pigment. They have an asexual cycle or schizogony and a sexual cycle or sporogony, which occurs in the erythrocytes of the vertebrate host In P *gallinaceum of chicks, the schizogony cycle has also been* shown to occur in the cells of the reticulo-endothelial system, but sporogon (sexual cycle) occurs in the red blood corpuscles only

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was given by Rogers

(1) Geographical Distribution

[illegible] from latitudes 60°N up to 30° to 40°S

The detailed distribution of malaria in Ind a is given [illegible]

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The d stribut on of malaria in India shows great divers ty because the cl matic feature of India are very diverse. The valley of Kashmir at about 4 500 feet above sea level strangly free from malaria but malaria exists in the Himalayas at Murree at—an altitu of over 8 000 feet.

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The Indus plain from the North Western Frontiar to Delhi shows negligible quarta malaria with benign tertian infection predominat ng in the spring and mal gnant terta ir autumn and early winter *It is the region of vast periodical epidemics caused by th* [illegible] *The Cangetic plain from Delhi to Calcutta is an area of modera*

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It has been rightly said that malaria is one of the greatest scourges of humanity It is a menace to any people or country in which it has a decided incidence In the number of deaths caused either directly or indirectly the sickness and suffering the loss of time and

(1) Geographical Distribution

Malar [illegible] des 60°N up to 30° to 40°S It is mainly [illegible] prevalent in sub-tropical and temperate [illegible] species of malaria is closely related to [illegible] malaria in general throughout the world [illegible] the summer mean isotherms of 60°F [illegible] mmer isotherms of 70°F, the distribution of *P malariae* shows a most curious and patchy distribution suggesting that this is a dying species *P ovale* and *P tenue* have a restricted distribution the former having been recorded in the East as well as the West (Tropical Africa and also in South America) while the latter has been found among aboriginal tribes in some parts of India.

The detailed distribution of malaria in India is given below —

The distribution of malaria in India shows great diversity, because the climatic features of India are very diverse. The valley of Kashmir at about 4 500 feet above sea level is strangly free from malaria but malaria exists in the Himalayas at Murree at—an altitude of over 8,000 feet.

The Indus plain from the North Western Frontiar to Delhi shows negligible quartan malaria with benign tertian infection predominating in the spring and malignant tertian [illegible] and earl[illegible] winter. It is the region of vast periodical epidemics caused by the

to high endemicity In the United Provinces benign tertian is the predominating variety

Chittagong hill tracts ... n Bengal incidence is —*P falcip* ... 123 per cent) In North Easte ... alley and at the foot of the H ... city with liability to autumnal increase

South of the Indo Gangetic plain in the belt of high land wh ch forms the northern escarpment of peninsular India the Vindhya the Arballi and Chota Nagpur there is a tract of extreme malarial prevalence especially towards the east In Madras Presidency along the Eastern Ghats the region shows moderate endemicity with areas of hyperend micity and a hyperendemic zone stretches along the Western Ghats to as far south as Travancore State The rest of the Deccan is an area of moderate endemicity

Distribution of the Parasite

Seasonal Variation

Regarding the distribution of the variet es of the parasite *P vivax* is the predominant species, but th s only applies to the spring and early summer months In autumn and early winter *P falciparum* usually becomes predominant This applies to all India generally

The distribution of *P malariae* in India is an interesting study it is minimal in ... ngly greater as one passes ... The fact that *Plasmodium* ... rated from the malarious ... hat its incidence gradually ... from the east.

Other Countries

Malaria occurs in Afghanistan Persia Mesopotamia Arabia Asia Minor Turkestan over a wide zone extending over Central Asia, Burma Siam China, Formosa, Japan and the Phillipines Certain islands in the Pacific like Hawai and Fiji which are widely separated from the mainland are free from malaria.

Malaria in Europe

Malaria existed in the lowlying parts of England and it occurred in Finland and the low lands of Germany in Denmark, South Sweden and Scotland Vast areas in Italy had become depopulated and were abandoned because of the heavy incidence of malaria Vigorous anti malarial measures have since been adopted and flourishing towns are now arising in areas like the Pontine marshes Greece and Southern Balkans were heavily ... ed. Malaria ... e the carrier ... widespread

Malaria has shown a striking recession in Europe during the last half century This

these countries

Malaria in Africa

Malaria is widespread in Africa The whole of the equatorial region down to the northern part of the Un on of South Africa and the northern coast down to the desert are affected Subtertian malaria is the commonest form in the cases of Northern Africa and East and West Afr ca. *P ovale* occurs mainly in Nigeria, Congo and Uganda

Malaria in America

Malaria occurs in the southern and middle States, in the Panama Canal zone and the West Ind es but is generally on the decline Malaria is endemic on the east coast of South America South of Riode Janero and inland along the great rivers and their tributaries benign tertian malaria occurs in the Andes at an altitude of 9000 feet and extends to the southern l m ts of Argent na

Malaria in Australia

In Australia malaria occurs on the north coast and in a mild form, the whole of New Guinea is infected Quartan malaria is fairly common in the South Seas and adjacent islands

ducks respectively Plamodia are amœboid organisms which inhabit the tissues and erythrocytes of the vertebrate hosts (man, monkeys, birds, cattle, etc), and produce a characteristic pigment. They have an asexual cycle or schizogony, and a sexual cycle or sporogony, which occurs in the erythrocytes of the vertebrate host In P gallinaceum of chicks, the schizogony cycle has also been shown to occur in the cells of the reticulo-endothelial system, but sporogony (sexual cycle) occurs in the red blood corpuscles only

The asexual cycle occurs in the erythrocytes, and, at least in some species it has also been shown to occur in the cells of the reticulo endothelial system Exoerythrocytic or tissue parasites have recently been demonstrated in mammals this stage is not pigmented since pigment is derived from heamoglobin of red cells It is possible that reinvasion of the ret
from the blood When sufficient numbers
in the blood febrile symptoms appear in the
able of infecting mosquitoes but will cause
are also formed in the red blood cells
When a female anopheline mosquito
ese latter undergo development in the
m of large numbers of sporozoites
the insect s salivary glands, and the
mosquito then becomes infective to man

It has
the grea est
a menace

ality
ong
the
invaliding and subsequent pension roll of
Malaria Commission sent questionnaires al
ments of countries infected with malaria

treated The total number of cases
ume of its geographical distribution
nd the disease is all over the world

(1) Geographical Distribution

Malaria reigns ove
up to 30° to 40°S It
is mainly a tropical di
lent in sub-tropical and
temperate countries a
of malaria is closely
related to the summer
in general throughout
the world is limited in northern and southern hemispheres by the summer mean isotherms of 60°F the distribution of *P falciparum* by the mean summer isotherms of 70°F the distribution of *P malariae* shows a most curious and patchy distribution suggesting that this is a dying species *P ovale* and *P tenue* have a restricted distribution the former having been recorded in the East as well as the West (Tropical Africa and also in South America) while the latter has been found among aboriginal tribes in some parts of India

The detailed distribution of malaria in India is given below —

The distribution of malaria in India shows great diversity because the climatic features of India are very diverse The valley of Kashmir at about 4 500 feet above sea level is strangly free from malaria but malaria exists in the Himalayas at Murree at—an altitude of over 8 000 feet

The Indus plain from the North Western Frontiar to Delhi shows negligible quartan malaria with benign tertian infection predominating in the spring and malignant tertian in autumn and early winter It is the region of vast periodical epidemics caused by the
Th G nge plain from Delh to Calc tta is an area of moderate

an and Avian Malaria Simian species
Since then several worl
of monkeys *P Knowle*
d into a *Rhesus monke*
and virulent infection w
For this reason Rhesus
ng the therapeutic efficie
ccessfully inoculated into human beings In man, one attack of monkey malaria absolute immunity against further inoculation with the same parasite

malarial parasite of birds are of particular interest in connection with the investiga Ross who traced them through all the stages of their sexual cycle in the culicine Avian Species

P. marcox species, y in the system en been ned

all mammals, such as bats flying foxes and squirrels often show plasmodial infection gard to large mammals plasmodia have been found in the Indian buffaloes Plasmodial s have also been described in the blood of lizards Other species

tors of Malaria The following points of practical importance with regard to the of malaria must be noted

Only some of the species of anopheline mosquitoes can transmit malaria

Only the female mosquito acts as a transmitter

In any locality only one or two species of the anopheline mosquitoes are responsible e transmission of malaria.

is last factor is important from the point of view of prevention Knowledge of eeding habits of the mosquitoes responsible in a locality and the adoption of such ng conditions may secure effective control over out of 43 existing species only 12 are capable are important —*Anopheles minimus fluviatilis hillipinensis annularis* and *pallidus* Indian mosquitoes

The question as to how long anophelines once d with malaria can remain infective to man has also been worked out by inoculation ments Infection could be produced by bites of *A punctipennis* up to 55 days after g on crescents, and sporozoites were found in it

(3) Epidemiology

here are three essential links in the aetiological cycle of malaria —(1) Man (the voir of infection) (2) malarial parasites (the causative parasite), and he mosquito (the transmitting agent) There are certain additional factors which are ial for the successful transmission of malaria, important amongst these factors being mounts of rain fall, the temperature and humidity and the immunity of population is in turn affected by famines, movement of the population and other economic tions Aetiological cycle Factors affecting Endemicity

Temperature

Malaria Problem in India

Intensity and virulence

It is true that in India there are few malarial foci where the same degree of virulence and intensity as it does for e. Southern Italy and Greece, but the disease is so prevalent an India taken as a whole probably is one of the most malarious world and the disease constitutes a major public health proble point of view of morbidity and mortality. The Annual Repo Health Commissioner with the Government of India shows t malaria accounted for about 1,567,000 deaths. During the la small pox and plague, the three infectious diseases which gener notice were together responsible for about 357,000 deaths each which is less than one third of the annual toll of life taken by

Mortality and Morbidity

National Suffering

Regarding morbidity it has been estimated that near about 100,000 from malaria every year. Besides causing an appalling mortality and m leads to retardation of national development in India. It reduces norma is the greatest factor in lowering the health, vitality and physical de people. This has the deplorable effect of hindering greatly the … of the affected people. The financial loss due to direct and indirect effec enormous. The financial loss to the individual and the family alone has at not less than 11,000 lakhs of rupees per annum. The financial a d e which the government and administrations have to bear through the ravages are enormous. The disease produces not only a decrease of revenue but al in the cost of administration. Malaria causes incalculable loss to agriculture, commerce mainly through its direct and indirect action upon the labour po

Economic Loss

Fortunately this is one of the diseases against which true specific remedies

(2) Aetiological Considerations

Historical

Long before the cause of malaria was discovered the disease could be successfully treated by cinchona alkaloids and Binz from his experiments with protozoa prophesied the discovery of an organism belonging to this order as cause of malarial fever. The prophecy was fulfilled in 1880 when Leveran the plasmodium in the blood of patients suffering from malaria. Leveran's f corroborated soon after. The different stages of development of the quartan p the blood were demonstrated by Golgi in 1885 and in the following year that of tertian parasite as well as its connection with the course of fever.

Regarding the transmission of the disease there was a popular belief in sev of the world that mosquitoes were responsible. King in 1882 gave a number o for believing that malaria was transmitted by mosquitoes and in 1894 Manson suggested that mosquitoes might be the vectors of malaria.

MacCallum (1897) observed the fertilization of the halteridium parasite in the the fertilisation of the macrogametes. Ronald Ross in 1897 described the develo the pigmented bodies now known as oocysts in the stomach wall of mosquitoes fed on malarial patients and later described the complete development of b d in the mosquito. In 1898 Grassi described the complete cycle of development o malignant tertian parasite in anopheles and also that of other forms. In 1900 … experimenting in England a malaria free country was the first to transmit malaria th bites of experimentally infected mosquitoes.

Malarial parasite and vectors

Human … …

The malarial parasite is a protozoon belonging to the genus plasmodium. The … malarial parasites are not capable of thriving in the blood of any of lower animals e… some of the higher apes, man is thus the only reservoir of infection of human malaria. T existence of three species i.e. *P. vivax* (benign tertian), *P. falciparum* (malignant tertia and *P. malariae* (quartan) is confirmed and recently *P. ovale* has also been desc… There is a tendency to further subdivide these recognised species into minor varieties, the plurality view has been recently strengthened by thousands of inoculations carried in the treatment of general paralysis of the insane and other nervous diseases. Ca… of the parasites have furnished additional evidence. Stephens has described *P. tenue* … Marchoux in 1925 suggested that each of the three recognised species of malarial para… exhibits different races and morphology with var… … non

Signs of a secondary anaemia of any degree may appear Reticulocytes which are the immature erythrocytes appear and there is a tendency of the parasites to attack these cells particularly of *P vivax* Megalocytes are rare, but basophilic granular erythrocytes are very characteristic of chronic malarial anaemia

Disintegrated red blood corpuscles are frequently seen in blood preparations in malaria some being present in the circulating blood and some are produced in the course of smearing Giant forms first described by the brothers Sargent are seen

An increased resistance of erythrocytes to saline solution in malaria infected persons especially more marked in malignant tertian and in chronic cases with enlargement of the spleen and liver has been observed The sedimentation rate of red blood corpuscles may be increased during the acute phase of the infection but becomes normal again with treatment

Blood platelets

During attacks the number of blood platelets is reduced later on, in the stage of leucopenia it is often increased

Haemoglobin

Reduction of haemoglobin is due to reduction in red blood corpuscles and the low haemoglobin content of the cells It seldom returns to the normal standard so quickly as the red blood corpuscles

White blood corpuscles

Changes in the white blood corpuscles and red blood corpuscles are useful chiefly for diagnosing malaria infections in chronic forms and when fever is suppressed by taking a few doses of quinine

A true leucocytosis occurs during the first few paroxysms, especially in malignant tertian infection but after several attacks leucopenia is characteristic of malarial fevers the number being generally between 3 000 and 5 000 per cubic millimeter of blood During the initial leucocytosis there is increase of the polymorphonuclear leucocytes, replaced later by mononuclear increase alone with the appearance of Turck cells and Reider cells Eosinophils decrease or disappear during the attack and increase in the interval even to the extent of producing a mild eosinophilia during convalescence

Phagocytosis

Phagocytosis by the white blood corpuscles is common in malaria It is particularly seen in the large mononuclear and transitional leucocytes and to a less degree in the polymorphonuclears Mainly portions of pigment are phagocytosed rarely especially in malignant tertian a phagocyte may engulf a red cell and its parasite or the parasite alone

Certain cells *e g* macrophages vascular endothelium etc which are absent from or are very rare in the blood of healthy subjects enter into the peripheral blood

Pigment

The true malarial pigment melanin or haemozoin is a black pigment formed from [illegible] he erythrocytes When the parasites [illegible] estributed in the walls of the blood [illegible] e grey to black discoloration of the

Haemosiderin a yellow pigment associated with blood destruction also appears in malaria It is found as granules specially in liver cells Kupffer's stellate cells capillary endothelia, spleen marrow kidney pancreas and occasionally in the white blood corpuscles

Spleen

During each attack of malaria the spleen is moderately enlarged sometimes painful and tender but soft. In an untreated case its edge can be felt on palpation a few days later

Early enlarge[illegible]
vascular tone
is great prolifer[illegible]
endothelial cells
cells of the pulp [illegible]

In chronic malaria the spleen be[illegible] d weighing as much as 2 to 3 lb [illegible] presents a slate grey to dark red [illegible] a of the tissue element a grea[illegible] of the capsule Sometimes peri[illegible] ises and later thickening of the [illegible]

Liver

In acute malaria the liver is frequently slightly enlarged and tender, a distended gall bladder and jaundice may be present In chronic cases it may be very large hardened and from brown to dark grey in colour Cloudy swelling of the parenchyma cells or fatty

Some of a s condar anaemia of any degree may appear ...

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... as 2 to ... to dark ... ement a ... ometimes ... ening of

Liver

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is also important although indirectly Malaria however may be present in the valleys of hills where the hill streams form a favourable breeding place for certain species of Anopheline mosquito In the Punjab where epidemics occur after every six or seven years the main factors according to Gill (1923) are —The high relative humidity resulting from heavy rainfall in July and August (2) A low spleen rate indicating absence of temporary immunity due to recent attacks of malaria (3) Economic distress and high price of food (4) The occurrence in previous years of outbreaks of malaria.

Endemic Indices

In estimating the prevalence of malaria in a locality determination of "splenic index" is helpful The term denotes the percentage of children between the ages of 2 and 10 years who have enlarged spleens due to malaria According to Stephens and Christopher the age limitation is important for among the inhabitants of a very malarious country the adults are more or less immune and their spleens are diminished in proportion The infantile spleen rate *per cent* is the basis of endemic malariousness of a locality

Determination of the parasite rate by the thick film method is of greater value in estimating the prevalence of malaria than the spleen index When twenty five or more slides of unselected village children under 10 years of age are taken and examined the percentage in which malaria parasites are found is termed the *endemic index* of the community Besides the spleen and parasite rates an endeavour should be made to ascertain the amount and severity of 'incidental malaria" among the immigrant population and the percentage of infection in anopheline mosquitoes (the sporozoites rate)

A number of methods of determining the degree of splenic enlargement *e g* that of Christophers Schuffners etc have been described

The most convenient method followed in the School of Tropical Medicine Calcutta, is to push the spleen as far as possible and measure the farthest point in inches from the tip of the ninth costal cartilage

e of Indices

It is necessary before undertaking a malaria campaign to estimate the amount of malaria present in the locality This is done by determining the following indices

(i) *The splenic index*, this is the percentage of children under 15 with enlarged spleen palpable below the costal margin.

(ii) *The splenometric index*, the projection of each spleen below the costal margin is measured in finger breadths and the average size of enlargement is determined It is particularly useful in assessing the value of antimalaria measures in places where the splenic index is high and the spleens are large Here the splenic index alone would not detect an improvement indicated only by a general decrease in size of the enlarged spleen if they remain palpable (iii) *The Parasite index* is the percentage of children under [illegible]

technique is recommended —remove the legs and wings of the mosquito, fix the [illegible] by transfixion with a pin seize the head with fine forceps and pull it off, two shining drops are visible at the back of the head these are the salivary glands spread them out on a slide sometimes the glands remain in the thorax

(4) Pathology of Malaria

Blood

od les

chronic cases it becomes very marked

...s of a secondary anaemia of any degree may appear Ret culocytes which are the ...e erythrocytes appear and there is a tendency of the parasites to attack these cells ...rly of *P v v.ax* Megalocytes are rare but basophilic granular erythrocytes are very ...ristic of chronic malarial anaemia

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...tain cells *e g* macrophages vascular endothelium etc., [illegible] ...very rare in the blood of healthy subjects enter into the [illegible]

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Haemosiderin a yellow pigment associated with [illegible] ...is found as granules specially in liver cells [illegible] ...leen marrow kidney pancreas and occas[illegible]

During each attack of malaria the [illegible] ...l tender but soft In an untreated case [illegible]

Early enlargement is an acute congestion [illegible] ...a cular tone The pulp looks black and [illegible] ...great prol feration of the reticulo[illegible] ...lothelial cells lining the s[illegible] ...ls of the pulp show similar change[illegible]

In chronic malaria the [illegible] ...ls or more and may extend [illegible] ...l or choc late brown [illegible] ...at thicken ng of the [illegible] ...splenitis causes [illegible] ...capsule and adhe[illegible]

In acute malaria [illegible] ...bladder and [illegible] ...from brown [illegible]

degeneration of the central areas of the liver occurs Capillaries are distended with parasitized erythrocytes macrophage and phagocytic endothelial cells The jaundice which is not infrequent may be of toxic or hæmolytic origin

In the brain parasite infected red cells especially those with mature schizonts have a tendency to cling to the sides of the blood vessels and gradual packing of the capillaries with these red cells and accumulation of pigment results in reduction of circulation, thombosis blocking of the capillaries and symptoms of malarial coma

The bone marrow is dark red in acute malaria In chronic malaria the marrow of the bones changes from yellowish brown to chocolate brown in colour due to the replacement of the fat by vascular tissue. Parasites are often found in the bone marrow

Generally the kidney shows little or no change though acute hæmorrhagic type of nephritis is one of the rare complications which is usually sudden in onset

Changes in supra renals are more frequent in severe malignant tertian infection The lesion generally is a hæmorrhagic necrotic inflammation of the capsule

There may be massing of parasites in the capillaries of the pancreas with small hæmorrhages and deposit of malarial pigment in the pancreatic tissue

The digestive organs do not usually show any special changes In case of localisation of infection local disturbances may occur and gastric secretion is generally deficient In the intestines capillaries of the mucosa and villi sometimes get blocked with parasitised erythrocytes leucocytes and phagocytic cells containing pigment producing small hæmorrhages and patches of necrosed epithelium

Emboli caused by parasites may be found in the heart and lungs The malarial pig mentation of the lungs results from migration of pigment laden macrophages

Malarial parasites and the malarial paroxysm

— ... associated with the asexual development of ... of parasites have been carried ... of parasite watched from day ... (1910) These authors define a ... ction rises above that threshold ... *nt—although infected—is afebrile* ... he threshold probably varies in ... asites (asexual forms) per cmm ... *iparum* the corresponding figure ... light rigor is present with counts ... between the number of asexual ... cht and Meyer, however consider ... onsequence of malarial parasite ... tes or the products of disintegra ... d into the circulation ... of opinion is that the ... *foreign proteins*

The three stages of malarial fever *viz* shivering fever and sweating stage can be correlated with three distinct phases in the development of the parasites During the onset of fever and during the shivering stage schizonts and young *trophozoites predominate in* the blood

... be seen in the peripheral ... ial organs ... trophozoite ... e parasites ... urer forms ... just before

... a ...

(5) Clinical Aspects

The incubation period in infection with plasmodium malariae (quartan) is 14 to 21 days in infections with *P vivax* (Benign tertian) 14 to 18 days in infections with P falci parum (malignant tertian) 8 to 12 days These data are based mostly on observations in experimental production of malaria, by inoculation of infected blood or by bites of infected

mosquitoes in human beings The incubation period however varies within wide limits and the primary attack may be delayed for weeks or months (latent infections) The factors influencing the incubation period are related both to the host as well as the parasite In the case of the host excessive physical strain mental worry exposure to chill, parturition and similar conditions that lower the general body resistance, help in shortening the incubation period and precipitating the attack. In the case of the parasite the number of sporozoites infected and the number of merozoites produced by a particular variety i e its rate of multiplication are the determining factors Acceleration or retardation of cycle may occur

(i) Acute pyrexial attack

Prodromal symptoms

The prodromal symptoms may be noticed a few days before the occurrence of the actual malarial paroxysm or just a short time before it These are sense of fatigue, malaise dull headache pain in the extremities pain over the spleen area epigastric discomfort anorexia and sometimes constipation Some or all of these symptoms may be present in a particular case. Occasionally initial fever may be the only sign as is the case with inoculation malaria The prodromal symptoms may not be noticed and sudden onset of a chill may be the first warning of the attack Those who have had frequent attacks of malaria easily recognise these symptoms and know that a paroxysm will follow

Paroxysm

Though the fevers produced by four different varieties of malarial parasites vary to some extent in their character there are certain features common to all of them The fever generally comes during the forenoon (more correctly between midnight and mid day) and this is a characteristic feature of diagnostic importance The patient is usually aware that he is going to have a chill in a few hours before its advent On an average the attack lasts from six to ten hours the cold stage occupying about an hour hot stage about four to six hours and the sweating stage from two to four hours (B T and Quartan)

Cold stage

The cold stage follows on the premonitary symptoms A chilly sensation spreads from the vertebral column to the limbs and jaw shivering next supervenes shaking the patient violently with chattering of the teeth The feeling of cold is so intense that the patient lies huddled up covering himself with all the available wraps The face has a pale anxious look, the lips and nails appear cyanosed and the skin exhibits the condition known as goose skin Respiration is shallow and quick and the pulse is rapid and small Nausea, bilious vomiting and severe headache are common The skin temperature is low but the internal temperature begins to rise and is the highest by the end of this stage (about 104°F)

Hot stage

The hot stage usually starts with a feeling of warmth and some relief from chill and shivering but soon the patient feels intensely hot The rectal temperature does not go beyond 103°F or so The headache continues the cheeks and the entire skin is flushed, and the eyes are congested The pulse is full bounding and rarely dicrotic There may be pain in the splenic area. Within 4 to 6 hours the temperature begins to fall rapidly and the sweating sets in Due to intense thirst the patient likes to take plenty of cold water

Sweating stage

The dry and hot skin become cool and moist Perspiration first breaks out on the forehead and gradually the whole body is bathed in a copious sweat which has a peculiar spermlike smell The temperature becomes normal or subnormal and the pulse slower and of low tension The patient feels comfortable and falls into a quiet sleep that may last for several hours

The paroxysm of fever leaves the patient somewhat exhausted and weak, but those who frequently get malarial attacks usually go about their work after the paroxysm is over

Course

After a few paroxysms, or after the disease has persisted for ten days or more the patient may get well without any special treatment Relapses occur in the majority of cases no method of preventing them has been discovered Like other protozoal diseases malaria is also a chronic disease but if there is no further infection it definitely cures itself after some years Spontaneous cure is relatively more rapid in subtertian (if the patient survives the acute attack) than in benign tertian and quartan malaria In the former spontaneous cure takes place in one to two years, in benign tertian in four or five years and in quartan possibly a little longer Malaria parasites do not remain in the blood beyond five years after continuous stay in a non malarious place During these years the infection persists, the patient may suffer from attacks of malaria as a result of anything that might lower his resistance viz an accident, shock, exposure to inclemencies of weather surgical operations, etc.

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Malarial parasites and the malarial paroxysm

The acute paroxysms of malarial fever are associated with the asexual development o the malarial parasites in the blood Enumerative studies of parasites have been carrie out on untreated cases of malaria due to different species of parasite watched from day to day throughout their illness by Ross and Thomson (1910) These authors define a 'febrile threshold for malaria if the intensity of the infection rises above that threshold the patient gets fever if it is below the threshold the patient—although infected—is afebrile (subclinical malaria) The actual numerical value of the threshold probably varies in different individuals With *P vivax* about 200 to 500 parasites (asexual forms) per cmm of blood appear necessary to produce fever with *P falciparum* the corresponding figur

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In malignant tertian, only in very severe cases the schizonts are seen in the peripheral blood as the asexual division of this parasite occurs almost entirely in the internal organs At the height of fever the schizonts are least numerous and the very young trophozoite forms are common During the sweating stage progressive development of the parasites occurs and this is completed in the apyrexial period Peripheral blood shows maturer forms of the parasite the trophozoites and schizonts in various stages of development just before and at the onset of the next pyrexial attack

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Paroxysm

Though the fevers produced by four different varieties of malarial parasites vary to some extent in their character there are certain features common to all of them The fever generally comes during the forenoon (more correctly between midnight and mid day) and thus is a characteristic feature of diagnostic importance The patient is usually aware that he is going to have a chill in a few hours before its advent On an average the attack lasts from six to ten hours the cold stage occupying about an hour hot stage about four to six hours and the sweating stage from two to four hours (B T and Quartan)

Cold stage

The cold stage follows on the premonitary symptoms A chilly sensation spreads from the vertebral column to the limbs and jaw shivering next supervenes shaking the patient violently with chattering of the teeth The feeling of cold is so intense that the patient lies huddled up covering himself with all the available wraps The face has a pale anxious look the lips and nails appear cyanosed and the skin exhibits the condition known as goose skin Respiration is shallow and quick, and the pulse is rapid and small Nausea, bilious vomiting and severe headache are common The skin temperature is low but the internal temperature begins to rise and is the highest by the end of this stage (about 104°F)

Hot stage

The hot stage usually starts with a feeling of warmth and some relief from chill and shivering but soon the patient feels intensely hot The rectal temperature does not go beyond 103°F or so The headache continues the cheeks and the entire skin is flushed and the eyes are congested The pulse is full bounding and rarely dicrotic There may be pain in the splenic area Within 4 to 6 hours the temperature begins to fall rapidly and the sweating sets in Due to intense thirst the patient likes to take plenty of cold water

Sweating stage

The dry and hot skin become cool and moist Perspiration first breaks out on the forehead and gradually the whole body is bathed in a copious sweat which has a peculiar spermlike smell The temperature becomes normal or subnormal and the pulse slower and of low tension The patient feels comfortable and falls into a quiet sleep that may last for several hours

The paroxysm of fever leaves the patient somewhat exhausted and weak, but those who frequently get malarial attacks usually go about their work after the paroxysm is over

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After a few paroxysms, or after the disease has persisted for ten days or more the patient may get well without any special treatment Relapses occur in the majority of cases no method of preventing them has been discovered Like other protozoal diseases malaria is also a chronic disease but if there is no further infection it definitely cures itself after some years Spontaneous cure is relatively more rapid in subtertian (if the patient survives the acute attack) than in benign tertian and quartan malaria In the former spontaneous cure takes place in one to two years in benign tertian in four or five years and in quartan possibly a little longer Malaria parasites do not remain in the blood beyond five years after continuous stay in a non malarious place During these years the infection persists, the patient may suffer from attacks of malaria as a result of anything that might lower his resistance, viz, an accident shock, exposure to inclemencies of weather surgical operations, etc.

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The bone marrow is dark red in acute malaria *In chronic malaria the marrow of* the bones changes from yellowish brown to chocolate brown in colour due to the replacement of the fat by vascular tissue. Parasites are often found in the bone marrow

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The three stages of malarial fever *viz* shivering fever and sweating stage, can be correlated with three distinct phases in the development of the parasites During the onset of fever and during the shivering stage schizonts and young trophozoites predominate in *the blood*

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mosquitoes in human beings The incubation period however varies within wide limits and the primary attack may be delayed for weeks or months (latent infections) The factors influencing the incubation period are related both to the host as well as the parasite In the case of the host excessive physical strain mental worry exposure to chill parturition and similar conditions that lower the general body resistance help in shortening the incubation period and precipitating the attack In the case of the parasite the number of sporozoites infected and the number of merozoites produced by a particular variety i e its rate of multiplication are the determining factors Acceleration or retardation of cycle may occur

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In malignant tertian malaria periodicity is difficult to observe The fever due to the subtertian parasite is of tertian type but each attack lasts longer (from sixteen to eighteen hours or more) so that the apyrexial interval between two consecutive attacks may be very short or absent. Although daily intermittent fever (quotidian) is quite common, it may be remittent continuous or very irregular The various stages are less differentiated. The rigor stage is relatively less marked, the pyrexial period lasts much longer The paroxysm of fever usually lasts twelve to fourteen hours and a second paroxysm often begins before the first has ended

In malignant tertain

The fever caused by *Plasmodium ovale* runs a particularly mild course and has a tertian periodicity It has been reported from Uganda, Nigeria, Congo and Cameroons The attacks begin in the evening or at night but this discrimination is not always possible The temperature curve consists of a series of high peaks on narrow bases showing tertian periodicity

P ovale

In malignant tertian fever the primary attack, unless it takes a turn for the worse and becomes pernicious is of about a week's duration even when untreated Towards the end of that period the temperature chart shows a characteristic "downward slope"—The first apyretic interval lasts only a few days and is followed by the first relapse which is often more severe than the primary attack but lasts about the same time Thereafter the patient (untreated) usually suffers from four or five relapses of declining severity at intervals of approximately ten or twelve days when the relapses cease for a considerable time Afterwards they come on only at irregular intervals and in less severe form The disease as a whole is less protracted and is often more quickly cured then is the case with other types

General course

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relapses vary between ten days and three weeks As time goes on although the relapses tend to recur less frequently they maintain for a year or more their original severity This quick disappearance of subjective symptoms after paroxysms is characteristic of malaria and is very different from the protracted feeling of ill health which follows recovery from even so short an illness as dengue and sandfly fever

In the great majority of cases of uncomplicated malaria the general course is towards recovery Persons who are repeatedly infected and reinfected often fail to make a sufficient recovery between their frequent attacks and they pass into a condition of Chronic malaria"

Mixing of the different malaria species frequently occurs generally at the beginning the asexual development of one species of parasite is suppressed by another and it is only after one species has been eliminated that the other succeeds in appearing In India mixed infections benign tertian occurs later on say in spring when crescent forms are often still to be found in the blood although in the acute stage the malignant tertian infection (late autumn) predominates

Mixed infect

Anaemia is due to the destruction of the parasitized red cells and its degree depends on the severity and duration of infection It develops rapidly and a peculiar pallor of the skin is asso
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Although all his cases were of the macrocytic type normocytic anaemia also has been reported by others There is no hypochromia, for the iron pigment liberated by the destruction of erythrocytes is largely retained by the reticulo-endothelial cells

Anaemia

In patients with malarial anaemia administration of quinine produces a rise in the reticulocytes in the blood which reaches its maximum in 4 to 7 days. This is called 'reticulocyte crises' and is believed to be specific of malarial anaemia. A sustained submaximal reticulocytosis is thought characteristic of persisting malarial infection

During each febrile attack the spleen becomes swollen, painful and tender and becomes palpable a few days after the onset In chronic relapsing cases, especially the ones that

Splenic enlargement

Benign tertian or *P vivax* infection is the common infection in the tropics and is the most predominant throughout the year in India. The shivering is less marked, the temperature rises very quickly is more prolonged and falls rapidly Headache, vomiting and pains in the limbs are worse than in quartan The onset of paroxysm is more synchronous

P malariae infection or quartan fever is generally the least common of the three types In the tropics it appears after the rainy season is over The paroxysms appear every 72 hours *i e* every fourth day from which the fever derives its name (quartan fever) Double or triple infections have been reported in which paroxysm occur on two successive days or daily paroxysms may occur Similarly mixed infections with different species due to sporulation at various intervals will result in an irregular or continuous fever

Clinically the premonitory symptoms are less pronounced the attack is more sudden and severe and the pernicious attacks are more frequent. Nervous symptoms and slight delirium are more marked during the febrile stage Abnormally high temperatures are reported but a sub normal temperature persist for a longer time during convalescence The paroxysm is *not so prolonged as in the benign tertian types and occurs most frequently during the* day i e late morning or the early afternoon On the whole the infection is more severe than bening tertian and has a higher mortality rate particularly in children

The incidence of *Malignant tertian* or *P falciparum* infection is much higher in the *tropical and subtropical regions* than in the temperate zones Cases may occur throughout the year but the highest incidence begins in the later part of the rainy season

The symptoms are more apt to be atypical and periodicity is difficult to observe The fever is of the tertian type but each attack lasts 16 to 18 hours sometimes as much as 40 hours so that the apyrexial interval between two consecutive attacks may be very short or absent The initial rigor may be very severe but is generally less marked often amounting to just a *chilly sensation only*

In some cases of malarial fever and these by no means the least dangerous—the subjective symptoms may at first be of so *mild a character that the* patient may be able to go about his duties with a body temperature of 103° to 104° These patients may not have any rigor or gastric trouble or any other disabling or distressing symptoms In some of these however the fever is liable to assume a pernicious character The diagnosis and proper treatment of these cases is therefore very important

(ii) Symptoms in detail

features of tertian
d falls rapidly

infection

In quartan type of malaria the paroxysms are of comparatively short duration and the ... above 102° to 105°F but abnormally high temperatures

(6) Diagnosis of Malaria

Clinical diagnosis

The clinical diagnosis of malaria is based on a combination of the following signs and symptoms (1) Intermittent attacks of fever, the periodicity varying according to the type of infection and the fever coming on with shivering and passing off with sweating (2) Early and marked anæmia. (3) Splenic enl[illegible] may not complain of fever but the tiredness a[illegible] splenomegaly should arouse a suspicion of mala[illegible] usually possible in a large number of cases but [illegible] of mistakes are commonly made, either a case [illegible] tropical fever (typhoid, kala azar, etc) or som[illegible] dengue, etc., may be diagnosed as malaria and [illegible] belief of a correct diagnosis may be confirmed In order to avoid such mistakes, endeavour should always be made to confirm the diagnosis by laboratory examinations.

Laboratory methods

Smear Examination—Most important laboratory method of diagnosis of malaria is examination of a blood film both thin and thick films being examined The diagnostic points are presence of the hæmozoin pigment free or within the white blood cells Other subsidiary points of sufficient significance are monocytosis, basophilia, polychromasia of red blood cells and leucopœnia pronounced leucocytosis repeatedly encountered definitely goes against malaria Finding of gametocytes alone does not neccessarily mean that the particular attack of fever is of malarial origin It may be some other fever superimposed over chronic malaria. On the other hand absence of malarial parasites does not exclude the possibility of malaria In low grade fevers with enlarged spleen peripheral blood may be negative probably due to the fact that the parasites are mostly in exoerythrocytic stage There are occasions when even an experienced worker may fail to discover any parasite in a case of malaria Given to a competent observer, examination of 100 fields of a thin film plus a reasonably careful examination of a thick film will enable a positive diagnosis to be [illegible]

factors in ensuring good results.

Concentration method—The concentration method of Bass and Johns is more tedious but the parasitized red cells are effectively concentrated and the red cells and parasites are perfectly preserved and stain as well as in ordinary thin films

Effect of Anti malarial drugs

[illegible]

therapeutically

Provocation methods

Provocation is sometimes employed to establish diagnosis particularly in cases of chronic splenomegaly The means adopted are cold or hot applications to the splenic area, exposure of spleen to ultra violet rays injection of some nonspecific protein such as milk, or administration of adrenalin by injection, etc. Pentavalent antimony compounds and salvarsan are also used for provocation but are not always successful

Sternal and splenic puncture

In atypical cases where routine examination of peripheral blood is negative, especially in subtertian infections, sternal puncture can be employed as a method of diagnosis. In the World War II many workers used this method and found it valuable The procedure is quite simple and can be carried out by means of a stout truncated lumber puncture needle Thick drop preparations can be made from the fluid thus obtained which contain larger number of parasites than peripheral blood Spleen puncture may occasionally be used as a means of diagnosis especially in chronic and relapsing cases due to *P vivax*

Complement Fixation Test.

Antigens prepared from organs rich in malaria parasites or red cells infected with plasmodia as well as prepared from artificial culture of the parasites, are used The test is performed as for the standard Wassermann reaction The test becomes positive in about

had little or no treatment, the spleen enlarges considerably and becomes hard. Acute splenic pain may be referred to the appendix region. Rupture of spleen as a result of injury may occur.

f the The liver becomes somewhat enlarged and tender, but functional disturbances are uncommon. Jaundice or an icteric tinge is frequently seen. The blood sugar is decreased suggesting an indirect, general damage of an infective toxic nature to the liver so that it is unable to store glycogen. Indirect Van den Bergh reaction is positive.

al During the attack, the mouth becomes dry and the patient feels thirsty, the tongue gets thickly coated, appetite is lost and digestion is often disturbed. The stomach may be displaced due to the enlargement of the spleen. In a large number of cases achlorhydria or hypochlorhydria is produced and in a small percentage of the cases hyperchlorhydria, but the acidity returns to normal after recovery. Nausea with or without bilious vomiting is common. Bowels are usually constipated but in pernicious malaria, diarrhœa simulating cholera or hæmorrhage from the bowels may occur. Cases with the clinical picture of acute hæmorrhagic pancreatitis are also reported.

Polyneuritis is not a common complication of malaria. Its occurrence would appear to be determined by the intensity of the infection and certain climatic conditions. It often comes on gradually at the beginning of convalescence. The importance of making an early diagnosis is stressed so that specific treatment may be adopted forthwith.

[illegible] as well as in the vitreous humour and in [illegible] it rarely persists due to optic neuritis, [illegible]

as in this condition [illegible] vessels are shrunken.

y Anginal pains may be caused by malarial infection and it has been said that 4 per cent of malarial cases die of coronary thrombosis. The incidence is higher with Italian or African strains of *P. falciparum* but with Indian strains severe cardiac complications are not common. Ordinarily the heart is not affected but in severe affections, cardiac weakness [illegible]

Malaria is said to produce frequent evidence of myocardial damage. It affects the blood vessels indirectly through its action on the vasomotor nerves and directly by the action of parasites on the vascular tissue cells. Loss of vascular tone and fall of blood pressure may occur possibly due to a lesion of the suprarenal glands. Bleeding from the vessels in different parts may occur, viz. stomach, intestine, brain, skin etc.

The organs of respiration are rarely affected in uncomplicated malaria. There may be slight bronchitis and dyspnoea may occur in cerebral type.

The patient has a pale and sub-icteric complexion with a tendency to patches of pigmentation. Herpes affecting the lips, mouth, face and frequently the ears is a common concomitant particularly of benign tertian malaria. Urticaria may occur. During the pyrexial stage there is often an acute erythematous roseola and purpuric or petechial hæmorrhages in the skin have been observed.

During the stage of shivering the urine is pale and quantity increases due to the contraction of cutaneous blood vessels. Later when the temperature begins to rise the quantity decreases, the specific gravity is raised, the colour is dark and the acidity is increased, due to increase in metabolism. The quantity is less during the sweating stage, the excretion of urea, chlorides, sulphates, urobilin, urobilinogen and bases specially potassium is increased during the cold and the hot stages but diminishes during intermissions though it may still be above normal standards. The phosphates in urine are diminished during the attack but increase during the intermission. Excretion of iron appears after the actual attack is over and continues for some days. Temporary appearance of serum albu[illegible] has been reported after several attacks. In severe cas[illegible] nular casts may appear. Malaria infection is sai[illegible] ritis in cases with mild urinary changes. Only in [illegible] urine is definitely associated with depression in [illegible] occasionally been observed in malaria, which disappears with qu[illegible], present in the urine in cases of jaundice. During convalescence there is polyuria with low specific gravity and increased excretion of chlorides and potassium particularly in subtertian fevers.

(6) Diagnosis of Malaria

Clinical diagnosis

The clinical diagnosis of malaria is based on a combination of the following signs and symptoms (1) Intermittent attacks of fever, the periodicity varying according to ... with sweating ... ria the patient ... nplexion) and ... te diagnosis is ... on. Two types of mistakes are commonly made, either a case of malaria is mistaken for some other tropical fever (typhoid, kala azar, etc) or some other tropical fever as sandfly fever dengue, etc., may be diagnosed as malaria and when the fever subsides, the erroneous belief of a correct diagnosis may be confirmed In order to avoid such mistakes, endeavour should always be made to confirm the diagnosis by laboratory examinations.

Laboratory methods

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Concentration method—The concentration method of Bass and Johns is more tedious but the parasitized red cells are effectively concentrated and the red cells and parasites are perfectly preserved and stain as well as in ordinary thin films

Effect of Anti malarial drugs

... therapeutically

Provocation methods

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Complement Fixation Test

Antigens prepared from organs rich in malaria parasites or red cells infected with plasmodia as well as prepared from artificial culture of the parasites, are used. The test is performed as for the standard Wassermann reaction The test becomes positive in about

two weeks and persists for abo... months It has been fo nd hat 81 6 percent mal al [illegible]

When clinical signs are suggestive of malaria but repeated smear examinations are negative culture method may prove of definite value Although it requires special laboratory technique it enables a correct diagnosis in a large number of cases which could otherwise not be diagnosed. It is particularly helpful in determining the species of the parasite and making diagnosis in cases where quinine has already been administered

In addition to a careful record of temperature and clinical examination the therapeutic test of quinine or atebrin is sometimes helpful in confirming the diagnosis It may however be mentioned that a positive test is not so helpful as the negative *i e* if actual administration [illegible]

fall of temperature in other fevers or there may be a spontaneous cure. For the purposes of therapeutic test quinine in doses of 10 to 20 gr a day, or atebrin in doses of 5 grains a day should be given for 4 to 5 days

One uncommon condition that may be confused with malaria is hæmolytic jaundice, and examination of resistance of red blood cells will decide the issue The resistance is definitely diminished in hæmolytic jaundice whereas it is normal or may even be increased in malaria Kala azar is also liable to be confused with malaria Marked leucopoenia with absence of marked reduction of eosinophils plus presence of L D bodies either in the blood or in puncture fluids obtained from spleen liver or marrow will decide the question There are many diseases which may show temperature curves like those of malaria *e g* Malta fever liver abscess endocarditis septic diseases bronchiectasis, hydronephrosis Hodgkin's disease leukæmias and many others A careful clinical examination supplemented *by an ordinary routine laboratory examination will enable a correct diagnosis*

(7) Immunity in Malaria

tal

It can be said in brief that congenital and racial immunity in malaria does not exist and the acquired immunity is partial and short lived and exists rather against the toxic *substances liberated during the infection than against the parasite itself New born babies* have been reported to be infected whether the infection is through the placenta or due to mosquito bites it shows that infants inherit no immunity from the mother

In highly endemic areas 100 per cent of the children have been found heavily infected with high mortality rate. This has been reported not only in India but also from heavily infected endemic areas in other parts of the world This epidemiological evidence too is against any congenital immunity in children

Regarding racial immunity epidemiological data again do not support the existence of such immunity In India in 1939 it was estimated that there were over 12 million cases of malaria and in Ceylon in the same year out of a population of 6 million over ... were treated for malaria Considering that although these races have encountered ... *child exposed* On the other [illegible]

Mode of production of Immunity

In a highly endemic area in one race all infants are infected. Some succumb to the disease, others due to reinfections and superinfections gradually acquire immunity and ... parasite rate falls in adult life The surviving group at adult age has ... lts are healthy ... an in children ... patients resume

normal work during intermissions which points to antitoxic immunity That a similar immunity is not present in the adult population of a non endemic area, because of the relative high incidence in adults, justifies the conclusions that the continuance of the highest grade of acquired immunity is dependent upon an adequate and more or less a continuous antigenic stimulation over a long period. This naturally will not decrease favourably the incidence and mortality in a non-endemic area where the epidemics occur after long periods In highly endemic areas although the majority of adults will escape, infant mortality due to malaria will always remain high

Therefore Sinton as a result of his experiments on rhesus monkeys with *P knowlesi*, and Wilson on human studies in natural infection, conclude that when infection is rarely acquired, treatment should aim at a racial cure where exposure to infection is frequent and continued, treatment should aim only at clinical cure of the attacks and should be intensive enough not to interfere with the acquisition of immunity, while clinical prophylaxis is advisable in temporary exposure to frequent infection *i e*, short stays in endemic areas.

Mechanism of immunity

Present view

The present view about the mechanism of immunity is that two factors are involved, (*a*) antiparasitic element whereby the parasites are kept at such a low level, that no clinical symptoms can be produced This is noticed in latent infections where an attack develops only in case of sudden lowering of general body resistance This mechanism is cellular, due to the phagocytic activity of the macrophage cells which though non specific and sluggish in their action in the beginning become very active and specific later

of euglobulins in the plasma while albumin and cholesterol are decreased

Malarial pigment is considered by some to possesses antigenic powers The immunity induced by *P falciparum* is more fleeting than that left by *P vivax* and is the most durable in the case of *P ovale*

Relapses

Relapses depend on the treatment carried previously They occur in regular sequence weekly or after three months Change of season, fatigue exposure to cold and heat, wetting injury shock dietary indiscretion alcoholic excesses etc bring about relapses Relapses frequently occur in the early stage of fevers such as typhoid, influenza etc The course of a relapse is like a primary attack

Mortality

Mortality rate on the whole is not high except in children Usually it is below 10 per cent but is high in epidemics being as much as 20 per cent or more Prognosis for recovery for primary attack is excellent even in falciparum if properly treated Relapse rate is highest in quartan (over 60 per cent), next in benign tertian (over 55 per cent) and least in malignant tertian (over 40 per cent)

2. Chemotherapy of Malaria

During recent years great progress has been made in the chemotherapy of malaria The following is a classified list of some of the important drugs

I *Cinchona derivatives* —

Cinchona alkaloids *e g*, quinine, quinidine, cinchonine and cinchonidine are

all more or less active Beside these there are alkaloids which occur in minute quantities which are also active *e g*, cupreines and cupreidines The amorphous alkaloids have no antimalarial action

II *Amino-quinoline and allied derivatives*—

Pamaquin (plasmochin or plasmoquine), which has a marked action on sexual forms and action only on the asexual forms of B T & *Quartan (probably in toxic doses)*, has no effect on asexual forms of M T

Chloroquine (Resochin, Aralen, S N 7618)—chloroquine, belongs to the 4-aminoquinoline series Their action is similar to that of mepacrine and they are said to be more effective, they do not give rise to discolouration of the skin. Chloroquin is said to be more powerful than atebrin Both Plasmoquine and chloroquine have actions on exoerythrocytic cycle

Metachloridene (SN, 11,437) is 2 metanilamido—5 chloro-pyrimidine is similar to sulphadiazine It is active against avian malaria, not so active against human malaria, it may prove active against quartan infection in man

Pentaquine (SN, 13276) belongs to 8-aminoquinoline series Its action is similar to that of pamaquin but is said to be too toxic for general use in India

III *Acridine derivatives* —Mepacrine (atebrine) and similar products

IV *Sulphonamide derivatives e g*, prontosil, sulphapyridine, sulphathiazole, etc, have a destructive action on the plasmodium Sulphadiazine has a more powerful antimalarial action than others The sulpha drugs though they have some plasmodicidal properties, have a number of defects which make them unsuitable for general use in the treatment of malaria

V *I C I Series* Workers in the laboratories of Imperial Chemical Industries took anilinopyrimidine as the basis Antimalarial activity was encountered in No 2666 (October 1942) in avian Malaria but it was not effective against human malaria

Modifications of its chemical constitution by addition of guanidine chain led to synthesis of No 3349 (July 1943) This showed marked activity against avian and human malaria Hundreds of more compounds were synthesized some of which had powerful antimalarial properties but were not satisfactory excepting No 4430 which was quite active No 4430 was superseded by 4888 or paludrine which is a double guanidine derivative and is superior to 4430 This compound is not toxic and has marked antimalarial properties in small doses It has also the unique property of being active against the extra erythrocytic forms

(1) Study of Action of Antimalarial Drugs

It will not be out of place to mention here the method by which the efficacy of the various antimalarial remedies is tested

(i) *Tests on the parasites of avian malaria—Type Proteosoma'* These tests were used as a routine laboratory practic
drugs to birds through an œsoph

toneally The blood used for infecting the birds is taken when the parasites have reached

After ascertaining the maximum strength of the solution which the bird is able to tolerate in the dose given, a series of experiments is made to ascertain whether this strength of the drug causes delay in the appearance of parasites in the peripheral blood, and, if so what further dilutions also cause a distinct delaying effect The period of delay is ascertained by examining thin blood films every day the first day on which parasites can be found being compared with the first day on which they can be found in untreated control birds In the control birds the parasites generally appear on the fifth day after infection. A drug is not considered to have a distinct therapeutic effect unless the delay in the appearance of parasites in the blood of treated birds is at least extended to the tenth day

Gametocidal action Test

(*iii*) *Tests* ... parasite commonl ... rice finches from ... the gametocytes (... non sexual cycle ... internal organs ... whether the drug ... naturally infected finches are selected and after having made a daily count of the parasites during a short period (four or five days) the birds are treated with the drug in the same way as in trials on 'proteosoma' parasites of canaries The effect of the drug is observed by noting whether the parasites disappear or are greatly diminished in numbers as a result of the treatment.

Monkey malaria Te

(*iv*) *Tests on the malarial parasites of monkeys* It has recently been found that several varieties of malarial parasites which occur naturally in monkeys in the Far East and in Africa can be utilised for experimentally controlled therapeutic tests of antimalarial remedies In particular it has been found that a species of malaria parasite occurring naturally in monkeys of the species *Silenus irus* when transferred by blood inoculation to *Silenus rhesus* or *sinicus* causes an acute infection which when untreated invariably ends fatally but when treated with quinine, is cured or can be maintained at a low parasite level for months In India this method is now being extensively used for evaluating the relative efficacy of antimalarial remedies

Human malaria Te

(*v*) *Therapeutic tests on induced and naturally contracted human malaria* Since ... endeavour should be made to imitate ... al condition is that the patients must ... ted mosquitoes and not by the direct

In general the only test which can be conducted on patients who contract their infection in the field is a test of the immediate therapeutic value of a short course of the drug to be tested in comparison with the immediate therapeutic value of the same course with quinine

(2) Study of Cures

(i) Natural cures

Gametocyte appearance

The life of a parasite depends on the life of the host if the host dies millions of parasites which are living in it die also There is a tendency in chronic protozoal infections for a condition of balanced equilibrium to be reached between the patient's power of resistance

(ii) Test on *P gallinaceum* in chick developed by the I C I Laboratories (See under Paludrine)

and the parasitic invasion This condition one may term 'immunity' or better tolerance In malaria the rate of multiplication is decreased by the formation of non multiplying forms (gametocytes) from merozoites or asexual cycle In untreated cases of malignant tertian infection the fever usually subsides as soon as gametocytes appear in the blood. Thus a patient suffering from malaria is after a fairly long period, cured of the disease without any treatment provided of course he does not get reinfection during this time Patients who leave the tropics are generally completely cured in about two years though here and there one comes across cases which persist for five years or more Natural cures are partially brought about by excessive gametocyte formation which so to say converts the asexual cycle to non multiplying gametocytes It has been demonstrated that when the asexual cycle of *P falciparum* is destroyed for example by quinine gametocytes still occur in the peripheral blood, the sexual forms are gradually destroyed though no further treatment is given

(ii) Artificial cures

These are produced by the administration of certain antimalarial remedies which act by destroying the asexual parasites but have less effect on the gametocytes The important factors concerned in these artificial cures are —

The rate of parasite multiplication—It is known that the subtertian parasite multiplies at the rate of 24 32 merozoites in 48 hours and is readily influenced by antimalarial drugs while the benign tertian parasite forms 16 to 24 merozoites in 48 hours and is not so easily destroyed A single *P vivax* produces 24 new parasites in 48 hours and at this rate of multiplication it can produce 250 000 000 descendants in fourteen days a number which would produce about fifty parasites per cmm of blood. This is a number which can be detected microscopically but which will not give rise to fever The next generation however will produce sufficient parasites to cause fever A remedy which kills 96 per cent of the parasites of the benign tertian form in 48 hours will not cure the disease for it will only prevent the multiplication of parasites and will not reduce their number As a matter of fact the rate of multiplication of parasites is somewhat less than that indicated above because as soon as the multiplication of the parasites is checked sexual forms appear and since these can only reproduce in the body of the mosquitoes they are inactive as far as the human body is concerned That the difference in the rate of multiplication is not the only factor concerned is evident from the fact that the quartan parasite has the slowest rate of multiplication *i e* 5 to 12 merozoites in 72 hours yet it is the most refractory to antimalarial remedies.

Rate of parasite destruction—The percentage of each brood of parasites destroyed by continuous administration of antimalarial drugs is the other important factor According to Ross a man of average weight (10 stones) has about 3 000 000 cubic millimetres of blood and allowing for 5 000 000 red blood corpuscles in each cmm there will be 15 000,000 000 000 red blood corpuscles present in the body If there is one parasite per cmm of blood it means 3 000 000 in the body The lowest number of asexual parasites causing fever has been calculated to be about 100 per cmm *i e* 300 000 000 parasites in the total quantity of blood In severe infections of malignant tertian type the number of parasites is considerably higher as many as 12 per cent or more of the red blood corpuscles being infected When the number of parasites falls below 300 000 000 they produce little or no symptoms—parasitic relapse Theoretically a single parasite would in three weeks time multiply

to improve symptoms greatly while it was being taken, but it failed to produce complete cure even after 6 weeks' administration Acton found the cure rate in benign tertian infection to be 20 per cent after one month's treatment with quinine.

(iii) Effectiveness of artificial cures

The antimalarial drugs produce an immediate effect which may be followed by partial or complete cure We will now deal with these different aspects of the artificial cure

(A) The immediate and relative effect of the remedy used
(B) Partial cures or relapses
(C) Complete cures or sterilisation

(A) *The immediate effects* The parasiticidal effect is studied by noting the rapidity

Disappearance of asexual forms.

vessels of the brain and intestines giving rise to pernicious symptoms When quinine is given the trophozoites disappear within 24 hours after the first dose, gametocytes are not affected at all as they have been found to exist for as long as 40 days after commencing treatment and they are still able to undergo sexual reproduction in the stomach of anophelines It has been demonstrated that if the asexual cycle is destroyed and the patient is put on ordinary tonic treatment (with no quinine whatever) gametocytes that are present either die of senility within a few weeks or are destroyed by the cells of the body the patient *undergoing a complete cure*

In benign tertian infections the asexual cycle takes place in the peripheral circulation ... within 24 hours after the first ... are *not* so easily affected, as ... not completely prevented, and a ... The gametocytes disappear from ... stant to quinine than malignant tertian gametocytes

The method of administration is an important factor in the rapidity of cure the intravenous method is the most rapid in action and next come the intramuscular and the oral routes. If during the course of treatment parasites reappear it is certain that either the patient is avoiding treatment or the interval between doses is too long or the alkaloid is not being absorbed.

(B) *Partial cures and relapses* The destruction of the asexual cycle by antimalarial drugs is a ... or a few ... to find out ... to give a ... (5 to 6 w... however cannot be attributed to insufficiency of treatment as in some of Acton's experi...

Relapses

of the parasites from destruction —

(a) *Production of resistant forms* Against this view is the fact that if antimalarial drugs are properly administered in adequate doses, they cause immediate disappearance of the asexual parasites from the blood It has often been stated that the first ...

Drug resistance of parasites

(*b*) There is another factor which may explain the cause of relapses after treatment. The parasites may take up their abode in the capillaries of the internal organs or in areas where body fluids do not freely reach them or the patient's powers of resisting the infection (immunity) may not be stimulated. The existence of back waters, such as the spleen and ... the tissues it does not penetrate ... the causes. In case of malaria ... an additional *schizogory* cycle ... oir from which the blood may subsequently get recompensated. A cycle of development has been demonstrated in the capillaries of brain in birds but not so far in man. However, it has been pointed out that in malignant *tertian infections schizogony occurs in the* deep seated areas but in spite of this quinine is quite effective and acts as a specific while in benign tertian where schizogony occurs in the peripheral blood it gives a lower cure rate.

(*c*) *Failure due to different strains of parasites*—A species may contain many immunologically distinct strains. In addition to immunological differentiation they show differences in other respects such as severity of the disease manifestations, response to drugs and number of gametocytes produced.

(*d*) *Failure due to non absorption of drugs*. Failure due to non absorption of anti malarial drugs owing to catarrhal conditions and inflammation of the gastro intestinal tract has been assigned as one of the causes.

(*e*) According to new concept the persistency of infections and malarial relapse are closely linked with the cycle of developement of the parasites in the fixed tissue stage or *exo erythrocytic stage. There seems to be little doubt that the cycle of parasite in the* human host is fa ... ted than was formerly imagined. It appears to be certain now that after ... ndothelial cells or fixed *tissue cells occur ... nct cycle of development* before they are ... *cytic cycle starts*.

The essential mechanism of relapse according to this conception results from periodic discharges of tissue exoerythrocytic forms into the blood stream. The persistency of an infection is an expression of the length of time during which the development in fixed tissues continues. The *P. falciparum* and the *P. vivax* behave differently with regard to their relapse rates and the duration of infection because of this factor. In *P. falciparum* the tissue development stage is short and there is more or less complete expulsion of the parasite from the fixed tissues. In *P. vivax* there is prolonged fixed tissues development and partial repeated expulsion of parasites and this leads to relapses. Even different strain of *P. vivax* may have varying degrees of fixed tissue stages and give rise to different clinical patterns, that is, some are more relapsing than others.

Most of the older antimalarial drugs *e.g.* quinine mepacrine and even the new drug ... tic forms of the older drugs plasmo ... xic the new drugs paludrine and ... be understood why permanent cure ... es occured

Conclusive evidence of fixed ... the recent studies point to it. It has been ... within half an hour and blood is non ... in the blood. This occurs on the sev... day in P. falciparum the parasites ap... ularity This preciseness in appearence ... lace in fixed tissues. Although exo erythrocytic cycle has not been demonstrated the experience in World War II has forced this conclusion.

reinfections

It has also been pointed out ... common in cases of benign tertian than in malignant tertian ... atient is important as some persons acqu... is factor also plays an important part in ... edispos ing causes *e.g.* excesses of any ... avoided. To refer to a non malarial area such as a ...

(iv) *Co plete Cure*

The following factors possil ly contril ute towards l rin ng abot t a complete cure —

Tre t of relapses

(a) *Response of tl e defensive mechanis n of the body* —Tl e effects of tl e drugs on tl e tissue cells of the host possil ly mak ng the erythrocytes noxiou ca s ng the pl agocytes to destroy the paras tes or perhap l y the format on of ant bod es

(b) *Sele tive action of drugs or erytl rocytic and exo erytl rocytic forms* — Py action of drugs both on the exo erythrocyt c and erythrocytic forms of parasites l y s ch dr gs as palu lrine plasmoqu n an l pentaquin

3 The Cinchona Derivatives

Tl e C nchona alkalo ds occur n the var o s species of two r l ac s gene a *C n hon* a l *Re r a* wh cl re n l geno s to the ea ern sl pes o the An le n So th Amer ca l etween the lat t des 10 N and 20 S C nchona comp ses about fo t spec es of e ergreen hrul s or trees wh ch grow solate l or small cl mps le e forest The a erage l eigl t at wl ch hey flo r h s a alt ude of 3000 feet to 0000 feet abo e the sea level Some of the pec es are fo n l as h gh as 11,000 wh le others as lo v as 500 eet Th trees may reach the l e gl t of 80 feet and are al ed for the r l ark wh ch con a n ce a n potent alkalo l

In r l r

C nchona l a k was firs l rought to E rope n 1630 an l was u d n the treatm e t ag e As early a 86 c nchona plantat ons were starte l the N lg H lls the spec e g ow ng l est be ng *C offic nal s* Plantat o s were al o e tabl she l n the H malaya S kk m near Darjeel ng an l n the Karen H lls n B rma The spec es gro ng he t ere were *C s r l ra* an l *C al saya*

Of tl e large n mber of pec es an l sub-spec es onl a fe v y el ls com merc ally alu l le l rks They are —

Spe es of n l ona

I *C off i l s* var *condaminea* *bonpland ana* *crispa* y eld ng crown barks

II *C s c r l a* (Pa on) y el l ng red l ark

III *C p tayens* et *C lancifolia* *C cord f l a* el l ng Columl ian red l rk

IV *C da* *C n rcantl a* *C perun a a* y el l g grey ark

V *C al saya* y el ng yell w l ark

The s cce l tran pla ta f c nch na y a f llowe l by a per od o researches a l exper nent to f n l the proper ays a d n ean f propagat ng the new plants In Java a l the var et es were fo n l to po ess a l w perce tage of qu n e w th the s le except n of *C off nal s* tl s ariety howe er l d not grow very well Tl e Cal aya var e e ga e tl e h ghest y el l of qu n ne the a erage qu n ne co tent be ng 6 per cent except o al

Ne er Pl n t on

Tl e max m m co ntent of the alkalo d occurs in trees between the ages of se en an l e t a ed spec es an l u n l e and c nch n ne *nal s* an l *C robusta* qu n ne yield has al

Cuprea cortex contains both cupreine and quinine and is obtained from *Remij pedunculata* and other species

The therapeutic effects of cinchona bark are due to the crystalline alkaloids present of these *quinine* is the best known while *quinidine, cinchonine* and *cinchonidine* have been used to a comparatively less extent in medicine The alkaloids are contained in the cellula tissue of the phloem In the leaves they are only present in small quantities but large quantities are found in the stem bark increasing from above downwards as the root i approached The alkaloids exist in the bark in combination with cinchotannic acid and quinic acid The former is oxidised by exposure to a red colouring matter which i present in large quantities in *C succirubra*

The bark is usually collected by felling the trees or by 'capicing' These methods are now largely employed in preference to other methods and the plantations are so arranged that every year a large area is matured and the trees are ready for cutting down The tree yield the maximum amount of alkaloids when they are 6 to 9 years old and it is abou *this time that they are cut down In Russia the plantation is allowed to grow for 2 or* years and it is then cut down and alkaloids are extracted The alkaloidal content by this method is low being not more than 1 to 2 per cent

Composition of Cinchona bark.—Pelletier and Dumas in 1820 isolated quinine from the bark and later quinidine cinchonine and cinchonidine were isolated In addition to these four alkaloids the bark contains many more alkaloids, these are divided into crystallisable and amorphous

The bark in addition to these alkaloids contains certain acids neutral principles colouring matter and traces of a volatile oil gum starch and other vegetable matter The ash 1 to 2 per cent consists mainly of calcium and potassium carbonates and a little silica

Extraction of Cinchona alkaloids The principal dried barks used for the production of quinine are —*C succirubra* (red cinchona bark) 1 000 gm of good bark yielding at least 50 gm of total alkaloids containing 15 gm of quinine sulphate *C calisaya* (yellow

The bark is dried and ground to a fine powder mixed with slaked lime which is passed through a seive of 40 meshes to the linear inch sufficient water being added to make it damp The addition of lime makes the subsequent extraction of the alkaloids easier The mixture is made into a thin paste with water and put into vats Caustic soda and warm paraffin oil are then added and the vats heated to 170°F with frequent stirring of their contents, these are then allowed to settle when two layers form the oil on the top containing the alkaloids and the exhausted bark below The oil is decanted off and mixed with dilute sulphuric acid which dissolves all the alkaloids The mixture on standing separates into two layers the acid liquor containing all the alkaloids in solution The alkaloids are then precipitated by adding caustic soda The crude total alkaloids thus obtained sometimes called cinchona febrifuge are further purified

(1) Total Alkaloids, Totaquina

Totaquina—The fact that the alkaloids of cinchona other than quinine possess therapeutic activities almost as great as quinine itself has increased the possibility of using total extracts of cinchona bark Such extracts which are obviously less expensive than the purified alkaloids were first prepared in India in 1874 from the red bark of *Cinchona succirubra* in which quinine constitutes about one third of the alkaloids present This powder was called quinetum or febrifuge By 1903 trees of *Cinchona succirubra* had become rare in India as attention had been focussed on the cultivation of *C calisaya* and *C ledgeriana* and their hybrids species in which the relative proportion of quinine to the other alkaloids is about 70 per cent *C calisaya* and *C ledgeriana* though they can be raised h . . . n the eastern Himalayas grow well in Bolivia and in Java Cinchona

. . . the extraction

or less similar

that somewhat

of q n e o tle o her alkal ds and not more tl 5 rer ce t and f poss b | eparel from the total scale t w ll necess ate tl there s as a rule more c v h the a ld t on of suff leen from t me to t me n xt re an l undoubtedly tlele s here s general a all forms of malar a. H were equally eff cac ous p g ven n ben gn tert an Wh le to taq na posses e l gl tly less eff c ent ne s ol u ly nd cated n uffer from malar al inf e poe a (1933) ts c ha totaqu na of type I has of e her *C si cc rubra* or *C rob sta*

Totaq na tuo types

Efficacy of totaq i na.

The co npo on of tl e two types of c nel ona febr fuge (Totaqu na) s gi en belo v — *Compos t on.*

	Totaq na Type I Made by extract ng the total alkalo ds from c nchona bark (C s cc rubra)	Totaqu na Type II Add t on of suff c ent alkalo ds to res lue of qu n ne manufacture
Qu n ne	25 23 per cent	14.79 per cent
C nchon ne	27 67 "	55 11 "
C ch d ne	34.13	7 10
Qu l ne	0.0	6.21 " "
To l ry tall sable alkalo ds	87 03	83 21
An orphous alkalo ds	8 86 "	10.47 " "
Mo ure	0 99 "	1 77
A h	0 63	2.13

(2) Alkaloids of Cinchona

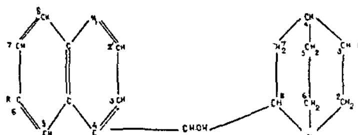
The fo r ch ef crystall sable alkalo ds der ed fron c ncho a ta k are qu n ne qu n d ne c cl o ne and c nchon d ne but over twenty o her alkalo ls mo tly unorphous have been sola e l from var ous spec es of c nchona and cuprea These alkalo ds are somet mes le c bed collect ely as q no d ne thorgl stric ly peak ng qu o d ne is the p tch l ke r l e left af er remo al of all the commerc ally valual le alkal ds from tl e total alkalo ds f c nch na bark.

C nchona alkalo ds

The f ur alkal d qu n ne qu n d ne c nchon ne an l c chon d ne form two pa rs f n e des of wh cl each member of the first d ffers from each member of the second tl l c f a me h xyl group—CH_3O

Const tut on

The f ll ng general formula s now ual y a s gned to th s group of alkalo ds (cf l al c 909) ha e Hu tenburg Schul ze and Volger 1931)



Qu nol ne r up—Se ond ry Al oh l gr up—Qu n l d ne group

In quinine and quinidine R=OCH_3 R'=$CH\ CH_2$

In cinchonine and cinchonidine R=H, R'=$CH\ CH_2$

In cupreine R=OH R'=$CH\ CH_2$

In the hydro bases R' becomes $CH_2\ CH_3$

In the alkylcupreines R becomes OAlK (homologues of quinine)

In the alkylhydrocupreines and alkylhydrocupreidines R becomes OAlK and R' becomes $CH_2\ CH_3$ (homologues of dihydroquinine and dihydroquinidine)

It is possible to divide the cinchona alkaloids into two series a dextrorotatory and a laevorotatory —

Chemical Name	Natural Alkaloid	Corresponding hydroalkaloid
Cinchonine Series—Dextrorotatory Alkaloids		
Cinchonine	Cinchonidine	Hydrocinchonine
Hydroxycinchonine	(Cupreidine unknown)	Hydrocupreidine
Methoxycinchonine	Quinidine	Hydroquinidine
Cinchonidine Series—Laevorotatory Isomerides		
Cinchonidine	Cinchonidine	Hydrocinchonidine
Hydroxycinchonine	Cupreine	Hydrocupreine
Methoxycinchonidine	Quinine	Hydroquinine

Modification of the cinchona alkaloids gives rise to a number of compounds of therapeutic interest Hydrogenation of the vinyl group and by replacement of the methoxyl group of quinine and quinidine by higher alkyloxyl groups the following compounds are produced When the Alkyloxyl group is

OCH_3 — — —	Methylhydrocupreine is formed
OC_2H_5 — — —	Ethylhydrocupreine (Optochin) is formed
$OCH\ (CH_3)_2$ — —	*iso* Propylhydrocupreine is formed
$OCH_2\ CH\ (CH_3)_2$ — —	*iso Butylhydrocupreine is formed*
$OCH_2.CH_2.CH\ (CH_3)_2$ —	*iso* Amylhydrocupreine (Eukupin) is formed
$O\ (CH_2)_5.CH\ (CH_3)_2$ — —	*iso* Octylhydrocupreine (Vuzin) is formed.

Optochin has a curative action in pneumococcal infections in mice, vuzin is toxic in vitro to Corynebacterium diphtheriae while eukupin and vuzin possess local anaesthetic properties

(3) Therapeutic Efficacy

While the introduction of atebrin like compounds and plasmoquin represents a notable advance in the scientific treatment of malaria quinine still ranks high in current practice on account of its clinical effectiveness, low toxicity and the widespread knowledge of its use and dosage

Of the natural cinchona alkaloids, very active in curing infections due to *Plasmodium cathemerium* in canaries was dihydroquinine followed by quinidine quinine cinchonidine and cinchonine in descending order The effect of hydrogenation has been shown to vary greatly for different alkaloids For quinine and possibly quinidine hydrogenation increases the activity, while for cinchonine the effect is probably to diminish the activity

No obvious relationship can be traced between optical activity and anti malarial action in the cinchona alkaloids

The anti malarial activities of the alkylquitenines have been investigated On oxidation

of quinine the inactive acid quitenine is formed Activity is restored to quitenine and the other analogous carboxylic acids derived from quinidine cinchonidine and cinchonine by esterification As the molecular weight of the alcohol used for esterification increases so does the anti malarial activity the maximum being reached at butyl or amyl quitenine after which there is a fall.

It is obvious that at present no precise general conclusions can be drawn as to the mode of action of the cinchona alkaloids as anti malarial drugs It is however generally agreed that the reticulo endothelial system may play some part in the process (cf Kritschewski and Demidowa 1934)

(4) Quinine Supply of India

Annual requirement

The number of individuals who suffer from malaria every year in India has been conservatively estimated at a minimum of 100 000 000 For the purpose of mass treatment the amount of quinine should be the minimum effective dose which would relieve the symptoms Taking this at 45 grains, a rough approximation of the annual requirements of quinine for India would be 100 000 000 x 45 gr or approximately 600 000 lbs The amount of quinine used in India is approximately 200 000 lbs If the above figure (600,000 lbs) of annual requirement of India be taken as correct (although the maximum figure given is 1 250 000 lbs) the present consumption in India is less than a third of the actual requirement

As regards the question of production of quinine India still produces less than half the amount of quinine annually consumed by her population Out of the total of 200 000 lbs 110 000 lbs are imported and only 90 000 lbs are produced in India (Figures according to Krishnan are the amount imported 140 000 lbs the amount produced 70 000 lbs)

Complexity of the Problem

The provision of adequate treatment for the malarious sick in India is a difficult problem Although it has been established that all the crystalline alkaloids of cinchona have a remarkable anti malarial action the importance of the fact has not been generally realized If the total alkaloids begin to be used in general practice the treatment of malaria could be made much cheaper and could be extended among the general masses

Extension of Cinchona Plan

In addition to this the question of extension of cinchona plantations has also been considered One of the arguments brought up against the extension is that in view of the rapid development of the synthetic anti malarials there will be no further necessity for cinchona alkaloids The author considers that unless something extraordinary happens during the next 15 to 20 years India will have to rely mainly on the cinchona alkaloids for the struggle against malaria The people in India prefer cinchona alkaloids to mepacrine and similar compounds Whether the new drug paludrine (4888) will replace cinchona alkaloids completely remains to be seen

Under the present conditions in this country therefore it would be very desirable to extend the cinchona plantations in India As regards the scope for increasing the production of quinine in India according to Krishnan the number of acres of land available for cinchona cultivation in India is 38 000 which can produce 6 840 000 lbs of quinine

I Pharmacological Action of Cinchona Alkaloids

To comprehend the rationale of the therapeutic action of these alkaloids it is important to have a clear idea of their general pharmacological action The type of action produced by quinine closely resembles that produced by the other alkaloids and it can be taken as a typical example of this group

The action of quinine is specially marked on leucocytes amœbæ and spermatozoa The action generally begins with *temporary* stimulation of activity of the protoplasm being quickly followed by inhibition of all vital processes and finally death Quinine probably forms a film on the surface which *decreases the permeability of the cell* thereby producing a narcotic action such as is seen on local application to nerve cells muscle cells etc All these effects give *this alkaloid the* property of being a general protoplasmic poison Its toxicity to vertebrates is however comparatively low The metabolic processes in the protozoal *organisms are retarded* Minute doses therefore merely produce slowing of the activities in the organisms while large doses produce first paralysis and then death Very dilute *solutions such as 1 in* 20 000 to 50 000 destroy amœbæ and paramœcia in a few hours and some pathogenic protozoa *e g* plasmodia The protoplasm in the amœbæ becomes granular *spherical* and in a few hours nothing but granular detritus remains this action occurs in the plasmodia in presence of the merest traces of quinine

The toxic action of quinine on the protoplasm endows it with bactericidal power but the action of the alkaloid on cocci and bacilli is somewhat varied Its germicidal efficiency is considered to be about half that of phenol, whilst its antiseptic action approaches that of mercuric chloride A dilution of 1 in 2 000 delays growth of bacteria and 1 in 800 inhibits the growth in fluids of organic matter and prevents lactic and butyric acid fermentation The drug also retards the action of many unorganised ferments

Some organisms are very sensitive to quinine and its derivatives while it has little or no action on others Moulds are most resistant to it in fact they thrive in solution of quinine sulphate About 0 5 per cent is required to stop the growth of putrefactive bacteria and 2 per cent to kill them Typhoid bacilli cannot grow in 1 in 30 000 solution Quinine has no direct influence on the course of most bacterial infections whether given by injection or otherwise

Some of the newer derivatives of cinchona for example the cupreines exert a powerful bactericidal action on certain micro organisms even in the presence of proteins and at the same time have a relatively low toxicity for the body cells This action as a rule increases as we go up the series from ethyl hydrocupreine to iso octyl hydrocupreine Thus quinine in 1 in 1 000 concentrations ethylhydrocupreine in 1 in 2 500 and iso octylhydrocupreine or vuzin in 1 in 60 000 concentrations will destroy *B tetanus* The same is true of streptococcus staphylococcus and *B diphtheria* with some reservations

Ethylhydrocupreine has a specially powerful action against experimental pneumococcal infection but unfortunately it has toxic action on the optic nerve and produces blindness even in moderate doses Iso octylhydrocupreine has a powerful action against streptococci and tetanus in septic wounds in concentration of 0 1 gm in a litre of water

(1) Action in Man

sensation
prolonged
ts are not

When taken by the mouth quinine acts as a bitter stimulates the gustatory apparatus and improves the appetite the peptic glands are reflexly stimulated In the stomach it is dissolved by the hydrochloric acid but it has no direct action on the flow of the gastric juice Given by the mouth there is little difference between soluble and insoluble salts as the alkaloid is converted into soluble hydrochloride and the less soluble salts are made more soluble by the gastr

The absorption occurs in
the first six hours after
with or soon after food
than the insoluble ones
hydrolysed by the alkali

Various digestive enzymes are affected to varying extents according to the degree of *concentration* of the alkaloids The activity of ptyalin the starch digesting ferment of the

action of pepsin is retarded in the presence of 1 1 5 000

The deduct of pract cal importance is that the t me of adm nis rat on of these alkalo ls relat on t meals is of the utmost importa ce They sh uld be adm n stered when they least interfere w th the act v ty of the gest ve enzymes that is abo t to 2½ hours after meals

Cir l tory s ste

Erythro ytes On the erythr cytes the aci l sal s of qu n e l ave a hæmoly t c act o *in v ro* an l blackw ater fever l as been attr buted l y some to the tox c effects of qu ne sa s o he red l lood cells Q n ne c rc lates n the l lood as q nine base Act n ha le n nstrated that strong solut ons of q ne and q n d e l ase such as 1 in 2,000 in r ormal ven after ce l nt n for fa nt hæmolys s n r n ous njections of strong s no loul t that r gors wl ch are son et mes ol serve l after s ch nject ons are d e to the hæmolys s thus produce l

Act n on the he rt The l eart muscle s acte l on n the sa ne way as the otl er muscular t e Very sn all q an t es accelerate tl e pulse and ra e tl e blood pressure large q a t es prod ce the reverse effect the act o is l rectly on tl e m tor apparatus f the l eart an l n t on the nerves Tl e depress o of tl e heart is re pon l le for the collap pr duce l l y very large loses pat ents suffer ng fro fe er Q n ne depres es solate l tr ps of tl e l eart of a turtle A frogs heart s weakene l by 1 n 50 000 solut on and 1 1 5 000 stops tl e heart n d astole n a few m n tes (large lo es of l gital s stop the heart n systole)

M ard n

Q n ne is con dered by some a hor ties to l e the greatest regulator n arrl ythm a lue to extra systole or aur cular fibr lla on It has been com ned w tl l g tal s n card a l eases for over a century Qu n ne and d g tal s are g en not only l ere arrhythm a s present l ut al o wl ere large doses of d gital s see n urgently neede l and where con co n tant l s urbances make qu n ne des ral le Q n l ne a dextro-rotatory somer of qu n ne l a lately been the s bject of much s udy ow ing to the ber efic al effects it prod ces n a r c lar fibr llat on and arrl ytl m a The rel ef afforde l by qu n n s bel eved t be pr duce l by the depres ant effect of the alkalo l o the heart n uscle wh ch prolongs the refract ry per od of tl e v c lar muscle th s way end ng the c rc s movements Th re luces tl e exc tab l ty of ventr cles and aur cles to a po nt below that at wh ch fi r llat on s pos l le Most of the c nchona alkalo d l ver the con ract l y of the car l ac muscle

Blo d press r The l lood pr ssure s lef t ly l were l af er tra eno s nject on an l Act n has po nte l out that th s lepress n mu l more m rked w th the lextro r ator ci ho ne ser es qu n d ne be ng tl e wor t offen ler n th respect

C en ntravenously these alkal ds ha e a l press ng effect on tl e re p ratory centres. Hy lrol ron des ha e a m ch weaker effect n th s respect tl an the hydrochl r des and tl erefore tl e e are preferred for n raveno s a lm n trat n It has been l wn that a ter lethal loses in cats (25 mgm per k lo body g t) tl e heart con nues to beat for two min es after stoppage of re p ra n

Resp rat on

On the cerel rum q n ne l as a le re ng effect though ot t cl a n arked degree as some of the other ant pyret c lr gs Beca se f its sedat ve act on n the central nervo s sy tem t l as been sed to induce sleep a few gra ns l e ng g en at be l t me Large doses may prod ce men al excitement s ch as tl at man fe te l n c nchon m When taken for prolonged periods it may g e r se to p ych cal dera gements In rare cases there is lo s of conscousness accompan e l l y del r um convul ons s por coma a l leath Weaken ng of the l eart is the ma n ca se of leath l t re p rat n stops before tl e l eart Death has been recor le l w h a 2 gm d e l ut as a rule fatal l se s 8 to 10 gm or more As q n ne is rap dly excreted recovery generall takes place l t deafness an l lefect in the s ght may rema n for weeks or even months In ord nary th rape t c doses t has n effect e her on the medulla or on the cord l t large d ses dep ess tl ese struct res an l l e re p ratory centre s espec ally attacked

Central nerv

Tl e c ncho a alkal ds an l the r der vat ves produce a sl w an l prol nged alo l on of se   n by the r d rect effect on the sens ty nerve end ngs For th s reason qu n ne is n t frequently em l ye l n tl e treatment f neuralg a Wh le 1 in 50 solut n of

Per heral

cocaine hydrochloride will produce anæsthesia of the cornea of a rabbit, *the same effect can be produced by* 1 in 60 of quinine hydrochloride, 1 in 100 of hydro-quinine, 1 in 1,000 of ethyl hydrocupreine (optochin) and 1 in 1,200 of iso-amyl hydrocupreine Quinidine and *cupreidine compounds* have also great anæsthetic properties but their action is somewhat weaker

Quinine is often combined ... is combination increases *its solubility and its p* ... ing compound is decidedly weaker and has t ... inine alone is used As a *rule 0.25 to 1.0 g* ... advantages of the cinchona derivatives in co ... are that (1) injections are painful, (2) *the induction of anæsthesia* takes longer, (3) they are more irritating and in stronger solutions may cause sloughing; (4) the anæsthesia produced may last for several days

Special senses The eye Quinine and its allied *compounds when given in toxic* doses, produce visual disturbances such as contraction of visual fields, diminution in acuity of vision colour blindness leading to amblyopia and amaurosis The development of the

The ear The common accompaniments ringing in the ears and deafness appear to be chiefly due to congestion of the blood vessels Sixty grains in 24 hours may cause marked disturbances in the ear and even *deafness In rabbits congestion and ecchymosis in the* internal ear were produced by giving large doses of quinine Degenerative changes have also *been noticed in the cochlear ganglia, otitis media may be set up by long standing* congestion and permanent deafness may be produced When giving quinine to patients *with middle ear disease,* the possibility of its activating a quiescent condition should be borne in mind

Quinine has a specific action upon the special sense organs the first sign of an overdose being ringing and roaring in the ears accompanied by slight deafness At the same time the eyes are affected, and there is diminution in the field of vision photophobia and even temporary blindness The effects are due to the action of quinine on the nervous elements in these organs

The metabolism is affected in a most remarkable manner by quinine in very small doses Interference with the activity of ferments is a *well marked property of quinine and* its inhibiting action on oxydases in the blood is well known Freshly excised still-living kidneys, perfused with blood containing glycocoll convert benzoic acid into hippuric acid, ... traces of quinine are added to the blood this synthesis is prevented. It ... many of ... ly to ... *ysing* ... ught ... iture, ... slight ... rease, ... ction

especially ... the by *decreasing* metabolism from its action on the muscles and ... the anabolic and katabolic processes of the cell, the processes of oxidation being thus *markedly* reduced For this reason, economy in the metabolism of the body as a whole is secured,

especially in those conditions in which katabolism has been stimulated by pathological

Effect on the body temperature

Effect on the muscle tissue

Quinine first causes a temporary increase and then a decrease in the absolute strength and the working capacity of muscle and finally death followed by immediate rigor Dilute solutions hasten fatigue The results are the same whether a muscle is curarised or not the action is therefore on the muscle fibres irrespective of their nerves On smooth muscle the effect is similar The total effect on muscle tissue with therapeutic doses is small

Uterus

Quinine has often been employed to increase the force of contractions in the second stage of labour, under the belief that it favours the contractions of uterine muscle, it is also believed that given in large doses it has an ecbolic action The action appears to be directly on the muscle fibres without the intervention of the nervous system as atropine does not modify its action According to some observers quinine inhibits the non gravid uterus and stimulates the gravid uterus because the distension of the fibres has rendered them sensitive to any kind of stimuli It should be remembered that high temperature

kills the fœtus Dilution of 1 in 10000 to 1 in 5000 may produce relaxation and paralysis Concentrations of 1 in 150000, such as occur in blood normally after ingestion of quinine in moderately large doses stimulate the intermittent contractions If now some exciting cause is present such as weak membranes or a patulous os the membranes may rupture and labour may be started

Spleen and intestine

In animals under anæsthesia injections of quinine produce a marked reduction in the volume of the spleen In pathological enlargements of this organ such as those occurring in malarial fever, administration of quinine causes contraction and reduction in its size These effects are probably brought about by the contraction of the involuntary muscle tissue in this organ The intestine may also be contracted

Fate of quinine in the body

Quinine is easily absorbed from the mucous membrane subcutaneous and muscular tissues and it circulates in the blood as quinine base The length of its stay in the blood is very short When quinine is given in large and continuous doses by mouth a concentration in the blood of from 3 to 10 mgm per litre can be obtained Doses of 2 gm a day [illegible] blood and when the [illegible] rise An intravenous [illegible] litre but the drug is [illegible], some is in the blood

corpuscles and some in the serum

Morgenroth's observation showed quinine is preferentially taken up by the red blood corpuscles, and in that position either kills the intra corpuscular parasites or exercises a repellant action on the merozoites *which are prevented from penetrating them and therefore perish.*

A lage proportion *(about 60 per cent)* after absorption is deposited in such organs as the liver, gall bladder, kidney supra renals lungs and spleen In the liver, the quinine

4 025 mgm, supra renal 7 02 mgm

Quinine occurs in the lungs in large quantities Experiments show that after ingestion per os or by injection, guinea pigs show a much greater proportion of quinine in the lungs than in the liver This is also the case with optochin and for that reason these compounds

, the greater part (60 per cent) is broken up probably by liver, most of the remainder is excreted unchanged in with the bile and traces may be found in the sweat an almost entirely by the kidneys When given by the mouth small quantities occur in the faeces but this is due to deficient absorption By the kidneys it is excreted unchanged and if this organ is healthy the process is very rapid,

by the mouth on an maximum complete s elimina (2 0 gm) two-thirds *24 hours*

There is difference of opinion re division of dose etc *on the rate of* hydrochloride and insoluble salts like urine The amount of quinine excrete *whether the drug is given by the mo* of opinion is that large spaced doses in the blood is reached in about six hours and the maximum therapeutic effect somewhat later It has been In nephritis and in ly some authorities vessels It is said *those due to anæmia and cachexia*

In malaria the excretion rate is similar to that in health but variations are greater after oral administration Quinine is excreted in milk (nursing mothers)

5. Therapeutics of Cinchona Alkaloids

The use of cinchona in the treatment of malaria dates as far back as 1657 *The ship* surgeons who visited India 1657 to 1801 used cinchna bark in the treatment of ague From 1804 to 1847 the cin and treatment by purgati meantime Pelletier (1820) of cinchona bark Subseq gradually took its place *In the meantime* other alkaloids such as cinchon and quinidine were discovered and in 1866 *the Madras Cinchona Commission* was appointed

to test their relative merits in the treatment of malaria The tests were rough and mostly clinical and the Commission came to the conclusion that quinine was preferable to the other alkaloids Next MacGilchrist (1914) tested a number of these alkaloids clinically and he placed them in the following order from point of view of their anti malarial efficiency —(1) Hydroquinine hydrochloride, (2) Cinchonine sulphate, (3) Quinine sulphate (4) Quinidine sulphate, (5) Optochin hydrochloride, (6) Cinchonidine sulphate

alkaloids (except cinchonine) more

The corresponding hydro-alkaloids

the environment is of very great

be employed rested between hydro-

ed that quinidine has a depressant

(1) Quinine in Malaria

Quinine and other alkaloid

Quinine still holds the foremost position in the treatment of malaria though the antimalarial value of the other alkaloids of cinchona bark is being more and more appreciated In considering the relative therapeutic value of the different alkaloids it is of great importance to take into account their effect in causing harm or inconvenience to the patient It may be said in favour of quinine

is therefore to be preferred

Quinine treatment of malaria is no *therapia magna sterilisans* However large and however frequent the doses, relapses are inevitable The malaria parasites are not influenced to the same extent at their various stages of development The youngest forms are the most susceptible and the gametocytes have the strongest power of resistance they are not noticeably affected in the body by the quinine

There is still a considerable difference of opinion regarding the methods of administration dosage and duration of treatment This is largely due to the varying incidence severity of infection and the resisting power of the several varieties of malaria in different parts of the world It is therefore very difficult to lay down any hard and fast rules regarding these points which may be of universal application

Duration of treatment

With regard to duration of treatment of malaria with quinine there are two schools of thought According to some authorities the relapse rate is not decreased by prolonged treatment with quinine and there is risk in giving a prolonged treatment According to others a prolonged treatment with 10 to 20 grains of quinine lasting for several weeks is advisable to eradicate the disease In the author's experience in India a short course lasting from 5 to 10 days with each paroxysm of malaria have been found to be satisfactory With the majority of patients in this country prolonged courses are difficult in practice and reduction of relapse rate with such courses is small We, therefore, advise treatment of every attack of malaria with 5 to 10 days of treatment with cinchona alkaloids

The *following* main principles may be laid down in the treatment of malaria with quinine

1 The alkaloid should be administered immediately after the diagnosis of malaria is assured irrespective of the stage of the disease and the height of fever

2 Quinine should be given by the mouth when it can be administered and absorbed by that route

3 The administration of the alkaloid must be continuous over a period of at least 5 to 10 days Some authorities recommend considerably longer courses but these appear to be unnecessary

4 Quinine will not act efficiently if the liver is *sluggish or congested* or *if the gastro intestinal tract is disordered* To obviate these difficulties a brisk purgative *e g* 2 to 5 grains of calomel or an ounce of castor oil should be given on the day on which the quinine treatment is begun Quinine should preferably be given in the form of solution and should be well diluted rather than in a concentrated form This will aid absorption and will prevent its upsetting the digestive functions *If tablets or pills have to be given they should be crushed* and given with plenty of fluid

5 *The administration of quinine should be so timed that it reaches the* blood stream at the moment when the latter is at its alkaline tide The portal blood stream reaches its maximum alkaline tide some 2½ hours after a meal

6 The alkaloid should preferably be administered with alkalies as these tend to increase the absorbing power of the intestinal mucosa for cinchona alkaloids from the small intestine

7 In the treatment of all cases of fever it should be remembered that it is wrong to continue giving large doses of quinine for many days if it is not producing any effect Quinine does good quickly if it is going to be of any use *at all Whether treating ordinary cases of primary attack or of relapse* it is seldom necessary or advantageous to give 20 to 30 grains of quinine daily for more than 5 to 10 days If the fever does not subside some other factor is responsible for its production and the treatment should be changed

The two plans for treatment of the disease are —

(*a*) Short course treatment It is believed long continued treatment does not prevent relapses and this is the view held by the writer so far as Indian malaria is concerned Medication for longer periods than 7 to 10 days is not recommended

(*b*) Prolonged course treatment After treatment of the attack the quinine is continued in daily doses of 7 to 10 grains for many weeks

The patient should be put to bed before the quinine treatment is started and he should be kept in bed for at least three days if not longer however mild the attack *may* be Fifteen to twenty grain quinine should be given daily divided into 2 or 3 doses according to the weight and age of the individual Some clinicians give the drug every six hours on the assumption that the action of a dose lasts for six hours As the febrile paroxysm which *follows sporulation of the* [illegible] begins between 2 a m and 12 noon it is held that doses should

Sometimes, quinine cannot be given by the mouth owing to persistent vomiting, especially in pernicious cases. In such cases the best method of administration is by the intramuscular route. Ten grains given in this way produce cessation of vomiting and other acute symptoms within a few hours, and disappearance of parasites in 18 hours. Quinine can then be given by the mouth.

Prolonged course treatment

The following plans have been suggested for prolonged treatment which is continued for weeks:—(*a*) 10 grains of quinine once daily. (*b*) 30 grains of quinine on each of two consecutive days, *e.g.*, Saturday and Sunday each week, the amount being preferably taken in 4 separate doses. (*c*) 30 grains of quinine once a week, *e.g.*, Sunday, in four doses. (*d*) 15 grains on each of two consecutive days, *e.g.* Saturday and Sunday each week. (*e*) 15 grains of quinine only one day each week, *e.g.*, Sunday. The amount in the last two plans is taken in one dose and is suitable for mild attacks. The daily dose plan would appear to be the best as it is difficult to state on which day the parasites will appear in the circulation in sufficient numbers to produce a paroxysm. Ten grains given every day will probably be sufficient to destroy the parasites in the circulation. Larger doses given at longer interval may compensate, but the chances of paroxysms recurring are greater. Such doses may not prevent reinfection of the patient, and whenever it is possible these should be prevented by other means. James (1922) laid stress on the time of taking quinine and considers that success of treatment depends on this. The dose, he considers, must be taken 2 to 3 hours before the onset of the febrile paroxysms. If a relapse occurs the whole course including the 5 days treatment of the attack should be repeated. The removal of patients from an endemic area to a better locality is often helpful. Patients suffering from malaria who do not do well in tropical climates immediately start improving when removed to a better climate. It should be remembered that removal to a very cold climate may light up an infection and bring about a severe relapse.

A number of standard treatments of malaria with quinine have been suggested to suit various localities.

(1) Ronald Ross (1921) advises during the first two weeks, 15 grains of the hydrochloride or sulphate of quinine daily, then 10 grains daily for six days in the week for eight weeks making a total of 690 grains. Benign tertian infections yield rapidly to this treatment as regards the febrile attacks but are more difficult to cure in the sense of preventing further relapses than the malignant tertian type. Twentyfour thousand cases treated by the Ministry of Pensions were cured by this plan.

(2) The United States Malaria Commission (1921) recommends 30 grains (2.0 gm.) quinine sulphate daily in 3 doses while the symptoms last and for 4 days after, this is followed by 10 grains every night before retiring for 8 weeks. In Palestine this course was insufficient to cure chronic cases. The Jamaica Tropical Diseases Conference did not consider it advisable to recommend this method for universal application.

(3) In South Africa, Pratt-Johnson and Gilchrist (1921) advise 10 grains of quinine 3 times a day for three weeks, then 10 grains twice a day for one month followed by 10 grains once a day for two months. They found the relapse interval was 14 days in benign tertian and 12 days in malignant tertian cases, the crescents disappeared on an average in 15 days with 25 grains of quinine a day.

(4) Panama Canal Zone Standard course (1925) is more drastic. The patient is given a dose of 2 to 3 grains of calomel followed by a dose of Epsom salts before the treatment is started. Fifteen grains of quinine are given three times a day until the temperature settles down and is normal for 5 to 6 days. Then ten grains are given three times a day for 10 to 14 days. This course cured the vast majority of malignant tertian infections.

(l) Synergist of quinine

Combined alkali and Quinine treatment

Acton (1921) first recommended the association of alkalies with quinine [illegible]

[illegible] ... They found by means of Sallant's clinical test of giving by the mo[illegible] bonate well diluted then 2 gm an hour later, fol'o

hour and testing the urine with litmus till it becomes alkaline, that there was acidosis in malaria Acton and Chopra (1925) showed that the administration of alkalies before quinine, increases its rate of diffusion through the mucous membrane of the intestines By a previous administration of alkali the concentration of quinine in the mesenteric vessels can be greatly increased.

Alkaline mixture A

Sodium bicarbonate	60 grains
Sodium citrate	40 „
Water	1 ounce

Quinine mixture Q

Quinine sulphate	10 grains
Citric acid	30
(Or Dilute Sulphuric Acid)	30 min
Water	1 ounce

All cases are given calomel and magnesium sulphate before the treatment for the first day of treatment 3 doses of A are given at 7-30 9 30 and 11 30 a m. half an hour after the last dose one dose of Q is given At 6 p m a further dose of A is given followed 15 to 20 minutes after by one of Q For the next 4 days one dose of A is given three times a day at 7 30, 11 30 and 6-0 p m, followed on each occasion by a dose of Q For the remaining 2 days one ounce of A is given morning and evening followed 15 to 30 minutes after by a dose of Q Controls were given mixture Q only but no alkali The total quantity of quinine given in 7 days was 180 grains and the criterion of cure was non appearance of parasitic relapse during 8 weekly examinations

Sinton (1930) expressed the opinion that a one week course suffices in the majority of cases Though a prolonged course of treatment gives a slightly higher rate of permanent cures the difference is not sufficient to warrant the extra time or expense He also recommends plasmoquin 0 015 gm daily throughout the course, to be given after food If a relapse occurs the whole course should be repeated for one week and continued for a second week with two doses instead of three

If the alkaline mixture produces gastric disturbances 2 drachms of sodium citrate in 2 ounces of water is taken slowly Alkali treatment can be combined with cinchona febrifuge In severe cases a dose of alkaline mixture followed by 1 ounce of quinine mixture 15 to 30 minutes later, may be given at once without waiting for the purgative, but in these cases alkaline treatment should be continued till the urine becomes alkaline In severe cases of malignant tertian malaria, the amount of sodium bicarbonate may be increased to 90 grains dissolved in two ounces of water

(1) With this treatment in Sinton s series 28 per cent of benign tertian relapsed as compared with 40 per cent without alkali treatment, whilst in case of malignant tertian the relapse rate was 15 per cent as compared with 79 per cent (2) Albuminuria is not seen if alkalies are combined with quinine (3) In case when quinine cannot be given by mouth due to attendant vomiting—administration of alkaline mixture makes this possible

Quinine and alkali producing substances (citric acid is converted into an alkali in the gut) can be prescribed in one mixture especially for outpatients in which it is not possible to carry out Sinton s treatment

Quinine sulphate	10 grains
Citric acid	30
Magnesium sulphate	30 „
Chloroform water	1 ounce

This mixture is given 3 times a day 2½ hours after food for one week The dose is then reduced to 1 ounce a day for further two weeks Citric acid is converted in the gut into carbonate and this acts as an alkali

After treatm

that quinine apparently produces little effect and the patients relapse In such cases a dose of Novarsenobenzol before quinine treatment is helpful to over come infection but this should be given with caution

Provocative agents

Believing that the appearance of parasites in the blood in chronic cases of malaria renders them more liable to the action of quinine, certain substances have been used as activating agents to produce malarial relapses for securing the reappearance of asexual parasites in the peripheral blood. For this liquid extract of ergot 30 minims, five doses in all, or thyroid extract have been suggested. Subcutaneous or intramuscular injections of normal horse serum, milk and strychnine nitrate 2 to 3 mgm are used application of X Rays, ultra violet rays, cold douches, ice, etc., These methods are not very reliable and the several days may elapse before the parasites a 1.0 mgm (1 ccm of 1 in 1,000) intramuscular results by producing a marked but temporary venous injections of neosalvarsan in doses of stibosan in doses of 0.25 gm are also effective.

Provocative agents

Ascoli's treatment—This method which was used in Italy consists in giving intravenous injections of adrenaline in increasing doses starting with 1/100 mgm then 1/90 and so on till a dose of 1/10 mgm is attained. The size of spleen is reduced and the efficiency of quinine in resistant cases is said to be increased.

(ii) Dosage

Dosage and of Admini

In non malarious countries very small doses such as 2 or 3 grains are given In tropical countries the tendency is rather towards giving too large doses It has been said that less than 20 grains of quinine in a day in an adult has no curative effect in malaria. This is not borne out by James observations with induced malaria who found that a few grains a day kept the patients suffering

should be regarded as the maximum dose Such doses always control malarial fever and when they do not either the drug is not being absorbed or the diagnosis is wrong

A maximum dose of ten grains of the sulphate or hydrochloride by the mouth, two or three times a day for an adult given for one week is quite sufficient to cure 70 per cent of fresh malarial infections Twenty grains a day are sufficient in most cases and in women and weak individuals fifteen grains will

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After treatment

After treatment is an important consideration in malarial patients treated with cinchona alkaloids At the end of a course the patient is anæmic and run-down and a combination of iron, arsenic and strychnine in small doses is often beneficial in building up the resistance of the patient and in the destruction of the remaining parasites not destroyed by quinine treatment In some cases it has been found that quinine apparently produces little effect and the patients relapse In such cases a dose of Novarsenobenzol, before quinine treatment is helpful to over come infection but this should be given with caution

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Provocative agents

[illegible] ntravenous [illegible] so [illegible] ncy

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to 30 grains by the mouth in 24 hours [illegible] should be regarded as the maximum dose Such doses always control malarial fever and when they do not either the drug is not being absorbed or the diagnosis is wrong

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suffice Larger doses, as a rule, have no advantage To be effective, however quinine must be in *the body in sufficient* concentration when parasites are most abundant, *i e*, at the beginning of an attack, before and during the shivering stage and immediately afterwards The old practice of giving an adequate dose four to six hours before another attack was sound, but the attacks do *not* always occur at calculated hour It is, therefore, advisable to give the drug in several doses distributed *over a number of days It is suggested* by some workers that after prolonged and continuous use of quinine the action of quinine may become *less effective*

In relapsing cases 5 to 7½ grains twice daily for one month in the case of malignant tertian *infections and three months in the case of benign tertian and* quartan infections are recommended by some Doses larger than 20 to 30 grains *daily* lead to toxic symptoms, especially in weak individuals and are an absolute waste of the drug The consensus of opinion at present is that a 7 to 10 days course of treatment with 20 to 30 grains of quinine according to the weight of the patient is sufficient in all forms of malarial fevers *If there is a relapse* the whole course should be repeated

The liver of rabbits is damaged by giving repeated intravenous injections of quinine the *cells of the parenchyma showing degeneration and fatty infiltration*, the same may *happen* in man with large doses of quinine Amounts larger than 30 grains a day are therefore *by no means devoid of danger Nierenstein (1920) stated that over 30 grains of* quinine per diem are liable to injure the kidneys and cause albuminuria It should not be *forgotten* however that acute and sub-acute parenchymatous nephritis may occur as an accompaniment of malaria and is readily benefited by quinine treatment. Massive doses also depress the cardio vascular system and retard development of natural immunity on which the cure of the disease depends (McCarrison and Cornwall)

Quinine should not therefore be given in doses larger than 30 grains daily even such small doses as 5 grains two or three times a day given under rigid supervision are sufficient to cure an attack in persons weighing 100 pounds *but such small doses* are not recommended for routine administration. It is preferable to give the larger doses already suggested, *i e*, 10 grains two or three times a day

(iii) Causes of failure of quinine therapy

If quinine is properly administered and absorbed it is bound to cure a large majority *of the patients The causes of failure may be* —

(1) *Use of insufficient doses Hospital mixtures supposed* to contain 10 grains to an ounce have been found to contain 1 to 2 grains in India. (2) Adulteration of quinine Quinine adulterated with lime, starch and other inert substances to the extent of 60 or 70 per cent has not infrequently been met with in India, this is also the case with tablets (3) Faulty preparation Tablets *may be prepared* with unsuitable media and may have a coating quite impervious to water (4) Some of the patients may not be taking the quinine prescribed for them owing to *their dislike or prejudice* against the drug and they may be deceiving the physician (5) Non absorption from the gastro-intestinal tract due [illegible] changes produced by the drug *itself or complicating* [illegible]

rid of it with difficulty (7) Resistance of [illegible] are known to be more readily influenced by therapeutic agents than others and [illegible] therefore req[illegible] more intensive treatment

When quinine is being administered the physician should make sure —

1 That quinine prescriptions are in full strength There is evidence that mixtures in India are sometimes much below strength

2 That the patient swallows and retains every dose prescribed and that he does not omit to take a single dose of the standard course given Many causes may lead to omission *e g*, vomiting may occur or the patient may wilfully reject a dose

3 That the patient is absorbing quinine or any other alkaloids given This may be *ascertained by testing the urine Take 5 ccm of urine boil and filter the albumin if present* and add a few drops of Tanret Mayer reagent A precipitate is formed if the alkaloid is being excreted in the urine The drug should be given in hospitals by a responsible individual who sees that the mixture is swallowed One or more of these factors may account for the failure of quinine to cure malaria. Intramuscular treatment may succeed in certain conditions when quinine by the mouth has failed for obvious reasons

(iv) Relapses

Relapse rate

Relapses occur frequently in spite of proper treatment with quinine Administration of iodides adrenaline sera or vaccines exposure to ultra violet rays excessive heat or cold bring about a relapse and should be avoided In addition to the selective action of quinine on the type of parasite involved, the chronicity or acuteness of the infection is an important factor Sinton and Bird (1929) found that quinine cured 76 per cent of primary infections, but in chronic cases it cured only 32 per cent the balance all relapsed Chronic benign tertian infections are more difficult to eradicate These results were corroborated by treatment of induced benign tertian malaria for the cure of mental diseases which was easily amenable to quinine, the relapse rate was only 1 to 3 per cent with 30 grain daily doses for three days The reason why primary infections of benign tertian are more readily cured than chronic infections is not understood, some observers have stated that the parasites become more resistant

Inherent resistance of any strains of parasites is denied and only an acquired resistance is accepted by many authorities This may occur partly through unsuitable treatment and partly through continuous hyper infection during quinine medication Resistance may also be symptomatic of causative factors such as fatigue malnutrition injuries and the like exercising a provocative influence on the patients system Relapses are to be expected sooner or later and especially in benign tertian and quartan infection though malignant tertian yields more rapidly to a single treatment The chances of cure are enhanced by using other available remedies When for example a relapse occurs after continuous quinine therapy, it may be treated with atebrine and if it occurs after atebrin it may be treated with quinine (Nocht & Mayer Malaria)

In the writers opinion every relapse whatever be the species involved should be treated immediately with full doses just as if it were the primary attack

Quinine F

So called Quinine Fever By this term is meant pyrexial phenomena without any or [illegible]

(2) Routes of Administration

Quinine may be given by the mouth, subcutaneously, intramuscularly, intravenously or per rectum By all these methods it is absorbed into the circulation

Oral administration On account of the convenience of administration, the oral method is the one of choice It may be given as a powder, in solution, in cachets or in the form of pills or tablets When given in solution it is more readily absorbed than in any other form and therefore, this is usually employed The usual mixture employed in hospitals is 5 to 10 grains of quinine sulphate with 5 to 10 minims of dilute sulphuric acid in an ounce of water Some prefer the bisulphate or hydrochloride, but these are more expensive There is no evidence to show that the soluble salts are any more effective than the insoluble sulphates, though the absorption of the latter is somewhat slower Tablets are more convenient and are less unpleasant than the solution, but they may not be absorbed

Even quinine in powder form is not recommended by many authorities The powder and tablets take a longer time to absorb than the solution, but whether given in solution or in solid form, the alkaloid is absorbed into the circulation quite readily The form of administration adopted should be such as to suit the individual patient Uncoated tablets whether of the sulphate or of the soluble salts, if fresh, are readily dissolved and are absorbed If there is any doubt they should be crushed and then administered Some physicians prefer to give quinine in solution during the stage of active fever and to carry on with tablets during convalescence

The clinical condition of the patient is the best guide in deciding what method should be adopted The condition of the tongue is an excellent indication of the state of the gastric mucosa In ordinary attacks the tongue is moist and slightly furred, and under these circumstances the alkaloids are absorbed very well from the gut If the tongue is dry, red and cracked, quinine is absorbed badly, and in such cases other means should be adopted Quinine is generally absorbed readily from the gut, even in cases of malaria complicated with dysentery quinine has been shown to be absorbed If nausea and vomiting are present or there is the bilious vomiting of malignant tertian infection, it is useless to give quinine by the mouth Vomiting may have to be stopped by adrenaline in doses of 0 5 to 1 ccm of a 1 in 1,000 solution, by the mouth Provided it is retained, quinine by the mouth is as efficacious as by injection Experiments have shown that in solution it is absorbed with as great rapidity and appears in the urine almost as rapidly as when given by the parenteral route It is, therefore, the safest and the best method except when its effects on the alimentary canal are not desirable

... to take This disagreeable taste can
dose By
owder may
Another

... from the blood, and cate

When more than one group of parasites are present as in malignant tertian infections ...of giving the drug at short intervals when the schizonts are very young ...s given when the schizonts are half ...s carry on to sporulation Quinine given during sporulation does not stop the paroxysms

Experience shows that best results are obtained when these alkaloids are given 2 or 3 times daily in adequate doses As the concentration of the alkaloid rapidly falls between 4 to 8 hours after ingestion it is considered advisable to administer the doses at intervals not longer than 6 hours

Quinine durin fever

The older writers recommended that quinine should not be given during fever and even now this idea prevails in the mind of the public There is no basis whatever for this belief Even high fever is not a contra indication for its administration In malaria quinine should be given regularly and continuously irrespective of temperature Quinine has been shown to be just as effective in the febrile period as in the non febrile period. It has also been said that quinine should not be prescribed with free organic acids as quinotoxin is formed which is very poisonous That is not true because quinotoxin is not a toxic substance

Rectal route

Fletcher (1924) has shown that absorption of quinine by the rectal route as judged by testing the urine with Meyer's reagent is poor irregular and unreliable He advises that it should not be given by this route if any other method is practicable

Subcutaneous injection

Subcutaneous route This method has been used though some physicians condemn it Subcutaneous injections are painful and liable to produce necrosis they are said to be followed by extensive and dangerous abscess formation and even tetanus On the other hand it is said by some to be perfectly harmless and ensures rapid absorption of the drug The manipulation is simple and can be safely entrusted to an assistant In Russia subcutaneous injections of 0 5 to 1 0 gm of quinine hydrochloride are given in all cases in combination with antipyrin and iodine Rarely subcutaneous tumours have formed after injections of quinine

Intracutaneous injections of 0 25 to 0 5 per cent solutions of quinine bihydrochloride have been suggested in the treatment of chronic malaria Very small doses of quinine given by this method are said to be effective on account of antibody formation but this is doubtful

Intramuscular injection

Intramuscular route This method of administering quinine is simple but it should be carried out with strict aseptic precautions and the skin should be throughly sterilised with tincture of iodine The usual indications for administration by this route are bilious remittent fever persistent vomiting drowsiness or mental affections, also when the quantity of the alkaloid available is small as during World War II

The syringe and the needles must be kept in absolute alcohol which is washed out with ether before the injection or they should be thoroughly boiled It is advisable to use ampoules or sterules but if these are not available the solution prepared for injection should be carefully sterilised Bihydrochloride of quinine preferably dissolved in distilled water is employed and it should be

thoroughly boiled Sergents advise that the strength of the solution should not exceed 3 per cent but injections of dilutions as weak as 1 in 150 are known to have caused extensive *necrosis of muscle and nerve tissue* If *bihydrochloride* of quinine is painful, solutions of urethane quinine or quinine and urea have been recommended It is preferable to use dilute solutions *i e*, *7½* to 10 grains of *the hydrochloride or bihydrochloride* dissolved in 3 or 4 ccm of 0 85 per cent saline rather than in 1 to 2 ccm, which is usually done More than two injections of 0 5 gm of quinine in a day should not be given After injection the part should be massaged and collodion applied The situations recommended for giving the injections are —

(1) *The gluteus maximus avoiding the line of the great sciatic nerve* This is the best situation the spot selected being about 2 inches below the middle of the crest of the ileum The needle should be introduced perpendicularly and *if the point strikes the bone it should be withdrawn about a quarter of an inch* and the quinine injected into the muscle Care should be taken not to inject any into the subcutaneous tissue, as this will cause pain stiffness and inflammation and very frequently an abscess

(2) The cellular and muscular tissue below and external to the apex or *angle of the scapula The advantages of this site are that the injections are* painless there is no danger of damaging important nerves, the operation is not visible to the patient and the solution is readily absorbed

(3) The vastus externus about its middle on the outer side of the thigh

(4) The deltoid muscle avoiding the line of the musculospiral nerve The best place is 2 inches below the acromion process

The injections should not be given in the same place every day as this may *produce necrosis and abscess* When the neighbourhood of a previously injected site is selected, inject in the circumference of a circle keeping at least half an inch away from the previous puncture mark It is advisable to stop the injections and *administer quinine by the oral route* as soon as the paroxysms have been controlled

The most suitable preparations of quinine for intramuscular injection are [illegible] se of their ready solubility These [illegible] nd are liable to produce pain This [illegible] grain with ten grains of the hydro

[illegible]

C[illegible]
efficacy[illegible]
should[illegible]
cases[illegible]
do not respond to oral administration

Acco[illegible] mutilation.
The drug[illegible] the mouth
nor is it[illegible] the tissues
into whic[illegible] weeks and
may rem[illegible] of bacteria
from the[illegible] *m injection*
near a [illegible] iently seen.
Injection[illegible] xcruciating
pain lasti[illegible] alleged that
quinine g[illegible] *riefly stated*
these are[illegible]

(1) Its action is said to be more rapid and more vigorous But it has been found that with intramuscular injections quinine appears in the urine (Meyer's test) on an average in 60 minutes while if taken by the mouth in the form of a solution it appears in about 30 minutes The action therefore cannot be more rapid

(2) The effect of intramuscular injection is said to be more prolonged It is believed in some quarters that quinine given by intramuscular route acts as a kind of reservoir and in this way a steady concentration of quinine is maintained in the blood. The origin for this belief is not known It is found by actually testing the urine with Meyer's reagent that by whichever route it is given, quinine disappears from the urine in about 46 hours. Experiments on guinea pigs show that a large amount of quinine is absorbed after injection and only a small fraction of the total quantity injected can be found at the site of injection

(3) It is said to have a greater power of preventing relapses Rennie and Acton (1921) found in a malaria depot in the Himalayas (Dagshahi) that the percentage of relapses was the same whether the quinine was injected or given by the mouth

(4) The therapeutic value of quinine given in this way is said to be greater A number of medical men believe in the superior efficacy of intramuscular injections, on clinical grounds Careful experiments have shown that there is little difference between the oral and intramuscular methods, if anything the advantage is with the oral method The reason for this belief probably i
has to be left to patients, who may or
Intramuscular injections are given by
quantity of quinine is introduced intc
that a mixture supposed to have ten grains of quinine has one or two so the only advantage of intramuscular injection of Quinine is that the administration of the drug is assured

Necrosis of tissues at the site

very marked and hæmorrhages were present in the substance of the muscles The bases of these alkaloids were found precipitated in the tissues, and muscles and fascia round

continuous injections at the same site gave rise to patches of necrotic tissue about the size of an almond but that there was no indication of pus formation In weak, anæmic and debilitated subjects such dangers may exist Fibrous tumours have occasionally been formed by irritation produced by quinine

Occurance of tetanus

Cases of tetanus have occurred after quinine injections, but these are generally due
by injection of quinine forms a suitable
h are taken up by the leucocytes from
ork of Gye and Cramer on kataphylaxis

Conclusion

It will be seen, therefore, that intramuscular injections of quinine should not be given lightly or without most rigid attention to efficient aseptic precautions, not forgetting that tetanus spores are not killed even at 100°C, for a certain length of time It is not justifiable to give quinine by this route in the treatment of ordinary cases of malarial fever when the patient can take the drug by the mouth It should be reserved for severe cases of malignant tertian malaria with gastrointestinal symptoms, where quinine cannot be given by the mouth, or in young children and fat patients where intravenous injections cannot be given because the veins are difficult to find It is true that hundreds of injections may be given without untoward effects, but the very next one may lead to

disaster Necrosis of the tissues is often a slow process and the results may not be apparent until weeks or months after the injections Intra muscular injections do not produce cinchonism on account of the slow absorption of quinine

Briefly stated, the dangers of intramuscular injections are (1) tetanus (2) necrosis and formation of an aseptic abscess and (3) injury to nerves

Intravenous method The indications for intravenous administration of quinine are firstly, appearance of a very large number of parasites in the blood such as a dozen or more in a single field and secondly, pernicious malaria with nervous or mental symptoms such as drowsiness aphasia and nervous twitchings

It is not advisable to give more than 0 5 gm of quinine in Indian patients by this route at one time Injections should be given slowly otherwise collapse may result Small amounts of quinine, even as low as 0 3 gm, are sufficient to produce immediate favourable results, large doses, *e g*, 1 0 gm do not appear to display any greater immediate effects In addition to intravenous injections 0 5 to 1 0 gm may be given intramuscularly In the large majority of cases temperature returns to normal on the second day and sometimes though less frequently, on the third day A sharp rise of temperature may occur after the injection probably due to the large number of parasites destroyed

Two methods for giving intravenous injection of quinine are recommended —

(1) By giving it in 4 to 6 ounces (100-150 ccm) of (0.9 per cent) saline The apparatus

too concen...

central nervous system Extensive experience has proved that the use of more than 100 cc fluid for each case as advised by some is unnecessary and not devoid of danger

... be given by means of a 10 to 20 ccm syringe 7½ to 10 grains of

The intravenous route is especially recommended in serious and dangerous malarial infections, *e g*, cerebral malaria, where the effect of the drug has to be produced in a very short time and a few hours' delay is likely to be fatal Many cases are lost owing to the hesitation on the part of practitioners in using ... and efficient method of controlling symptoms in grave cases

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should be given in such a way that they reach ...

Experiments on rabbits show that there is considerable difference in the minimal lethal dose of quinine, according as to whether it is given well diluted and slowly injected or given in concentrated form and injected rapidly The minimum lethal dose by the latter method is much smaller

adrenalin solution to counteract the fall of blood pressure but it seems to unnecessary except in very severe cases of pernicious type In some patients rming symptoms appear in spite of all precautions If the pulse becomes ble give strophanthin or digitalin If the injections are given slowly in a umbent posture the dangers of cardiac syncope are considerably reduced

Disadvantages

It has been demonstrated that large doses of ordinary quinine salts *e g*, inine hydrochloride, when given intravenously are dangerous to life the spiratory centre being more gravely affected than the cardiac centres Quinine id hydrobromide in 7 to 10 grain doses is less toxic to the respiratory centre an the acid hydrochloride and is preferred Injections should be controlled blood pressure observations especially in weak patients It has been found experimental animals that if intravenous injections are given continuously rcumscribed areas of necrosis appear in the adrenal cortex Though the action quinine injected direct into the blood stream is quicker than that of quinine ven by the mouth or by the intramuscular method it has no greater effect in stroying the gametocytes or eradicating the parasites from the body and so reventing relapses Its action is more fleeting than when the drug is given y any other route and for this reason unless the administration of a dose is med correctly in relation to the parasites it is wise to supplement it as soon as ossible by doses given orally There is considerable evidence to show that uinine has little effect upon parasites contained in the red blood cells which are ying more or less stagnant in the small capillaries of the internal organs It is *hiefly effective against parasites which are free in the circulation especially* hen carried to the peripheral parts of the body

Dangers

isappears from the blood in a minute and during that time it circulates in the blood in maximum concentration and has a destructive action on those parasites which have not eached the safe areas within the erythrocytes

Routine Treatment

Cantlie and Moubarek (1924) in the Sudan treated a large number of cases of malaria y intravenous injections of quinine They gave 9 grains of bihydrochloride every day till he temperature became normal as well as ten grain doses of bisulphate by the mouth The injections occupied 30 to 45 seconds the pulse was accelerated 5—17 beats per minute or not more than 3 minutes Tingling in the mouth ringing in the ears sometimes onstriction of the chest rarely vomiting and on two occasions fainting occurred Their observations showed that the action was more powerful and thereby the stay of the patient n hospital was cut short, but the relapse rate was 42 5 per cent In another series of 1 103 cases there was a relapse rate of 77 per cent after 6 to 8 injections in each case. A dose of 0 5 gm of quinine given intravenously is as effective as 1 5 gm by the mouth If given on a fever free day in benign tertian malaria the paroxysm of the next day was cut short in 85 per cent of cases against 64 per cent with oral administration Injections are also said to be effective in chronic malaria when administration by the mouth is not effective Thrombosis of the vein often prevented the continued use of this method

Conclusions

Intravenous injections of quinine should therefore be reserved for cases of special urgency such as cerebral malaria with delirium and coma or malarial hyperpyrexia or malaria of pernicious type with persistent vomiting They should

be given without hesitaton in such cases and as soon as the condition of the patient allows it oral administration should be started

Cordes (1928) treated 14 cases of cerebral malaria with 7½ grains (0 5 gm) of quinine in 10 ccm of water and saved all of them In such cases puncture of the cisterna magna at the base of the brain and removal of 50 ccm of cerebro-spinal fluid is probably preferable to lumbar puncture Cases with as many as 40 per cent of the corpuscles parasitised have been saved by injection of 15 grains of quinine daily for three days Attention should be paid to the following points when giving intravenous injections

(1) As they produce a fall of blood pressure and affect the respiratory centre they must be given with the patient in the recumbent posture (2) The ... in otherwise it will produce ... vein or slips out stop the ... suck back into the syringe all the solution that may have escaped into the tissues round the vein (3) The injection must be given very slowly at least 20 to 30 seconds being taken for the injection of each ccm (4) The solution should be freshly prepared

The injections are followed by a transient feeling of dizziness lasting a few seconds while quinine can be tasted in the mouth before the injection is completed It should be remembered that while intravenous quinine therapy is a useful addition in the treatment of critical attacks of malaria it is useless in the prevention of relapses and fails to rid the patient of parasites completely

Intravenous administration of quinine should be given with caution when there is albuminuria severe jaundice organic disease of the heart marked anæmia or debility and idiosyncracy to the drug

Summary The best method of giving quinine is by the mouth and this is borne out by hæmatological as well as other evidences It is best given in solution but owing to its very bitter taste vomiting may occur Cachets are expensive but tablets if properly prepared are quickly absorbed after oral administration they are convenient and cheap for routine treatment and for control of malaria on a large scale Their therapeutic effects are not inferior Subcutaneous injections find few advocates Intramuscular injections should only be tried in those cases when the alimentary canal cannot tolerate quinine by the mouth Under no circumstances should these latter be used for routine treatment of ordinary cases where quinine can be give[n] ... tions are preferable for severe and urgen[t] ... no better results than any other mode of ... the case will have to determine which ... particular case

As regards the time of administration of the alkaloid we have already remarked that if quinine is given soon after a meal it hinders digestion by inhibiting the activity of the gastric and other ferments It is advisable to give it 2½ to 3 hours after a meal when the gastric contents are acid the digestion has been completed and the stomach is nearly empty If given at this time it rapidly mixes with the contents of the stomach and passes into the small intestine from which it is rapidly absorbed into the circulation. There is also less liability of its producing irritation of the stomach which it undoubtedly does when given on an entirely empty stomach early in the morning or a long time after a meal James prefers to give quinine 2 to 3 hours before the paroxysm of fever is due Intramuscular injections may be given at any time but it is preferable to give intravenous injections when the stomach is not loaded

(3) Other Cinchona Alkaloids in Malaria

Quinine till quite recently has been employed in the treatment of all forms of malaria, but Acton has shown that while it cures 90 per cent of malignant tertian infections if properly given in the benign tertian infections the primary cures were not more than 30 per cent even after a two months' course Cinchona febrifuge which contains all the alkaloids of cinchona bark gave a cure rate of about 50 per cent so that it can be reasonably concluded that there must be alkaloids other than quinine, which are responsible for this enhanced rate of cures These other alkaloids were tested individually Cinchonine and quinine in ten grain doses twice daily showed a cure rate of 60 per cent of benign tertian infections after a short course of three weeks

Fletcher tested the action of different cinchona alkaloids individually in the treatment of malaria his conclusions are as follows —

Efficacy of individual alkaloids

(1) In doses of 10 grains twice a day the 4 alkaloids i.e quinine quinidine cinchonine and cinchonidine appear to be of equal value in bringing about the disappearance of malarial parasites in patients weighing 100 pounds

(2) None of these alkaloids produce toxic symptoms when given in this quantity not even cinchonine and quinidine

(3) In doses of 5 grains twice daily cinchonine does not appear to be quite so potent as quinine and quinidine

(4) Cinchonidine sulphate is definitely inferior to other crystallisable alkaloids when given in small doses

(5) Quinidine sulphate acts better on the quartan parasites than quinine

(6) Quinoidine in 5 grain doses does not cause the disappearance of the parasites in 10 grain doses it cannot be tolerated as it produces severe nausea vomiting and collapse

It would appear from this that there is little to choose between the different crystalline alkaloids of cinchona bark so far as their action on benign and malignant tertian parasites are concerned Fletcher s conclusions regarding the toxicity of quinidine are not borne out by our experience It is liable to produce depression of the heart and fainting and sudden deaths have been known to occur, especially in those suffering from emaciating diseases such as kala azar

It is evident that much waste has resulted in using only pure quinine and cheaper and equally efficacious alkaloids might well be substituted in the treatment of ordinary cases of malaria while the more expensive and refined alkaloids may be reserved for severe types of cases

Dale and James (1925) found the curative effects of quinine quinidine and cinchonine is the same on all forms of malaria and except for the depression caused by the last there was no difference in toxicity Ciuca (1925) made similar comparative tests with quinetum which is a form of cinchona febrifuge containing all the alkaloids but only 15 per cent of quinine and 5 per cent of quinidine He found it to be as effective as pure quinine hydrochloride In bird malaria the results with cinchonine cinchonidine and quinidine ran closely parallel with those obtained in man Sergents and Catnei (1925) found cinchonine and cinchonidine effective in removing malarial parasites from the blood and in reducing the size of the hypertrophied spleen they found cinchonidine more powerful *than cinchonine in splenomegaly The Malaria Commission of the League of Nations (1927)* stated that in doses of 1 0 gm daily, quinine quinidine and quinetum are equally efficient in producing a clinical cure in malaria Cinchonidine in doses of 1 5 gm equals the efficacy of other alkaloids

Quinidine The data available are not sufficient to justify a definite pronouncement whether quinidine is in all respects an efficient and quite satisfactory substitute for quinine against malaria. It has been considered by some to be as prompt in its action against benign and malignant tertian as quinine and as well borne while others did not consider

it quite equal to quinine especially *as regards preventing relapses*, it was prone to cause more nausea Fletcher (1925) considered quinidine as good as or even slightly better than quinine bisulphate in its effects Sinton (1930) however thinks that quinidine has no more marked effect in producing a permanent cure in *benign tertian malaria* than has quinine Quinidine is more expensive than quinine and has a more toxic action on the heart and this limits its use

Cinchonidine Cinchonidine sulphate *is the least* toxic of all the cinchona alkaloids. Investigations of Fletcher and others have shown that in 10 grain doses twice daily it is almost as effective against malaria as quinine and on account of its lower toxicity it is well borne

Cinchonine Fletcher (1925) investigated its effect on behalf of the Medical Research Council and came to the following conclusions —

(1) Cinchonine in doses of 0 1 grain per kilo body weight is less efficacious than quinine in reducing fever, and in clearing malaria parasites from the peripheral blood

(2) *Cinchonine in doses of 0 1 grain per pound weight of body is as effective as quinine.*

(3) Cinchonine is not more toxic than quinine

Quinoidine This name has been given to the combined amorphous alkaloids which remain after all the crystallisable alkaloids have been removed from an extract of cinchona bark. Acton (1920) and Fletcher (1923) showed that it has no appreciable effect against *malarial parasite in 5 grain doses twice daily*

In view of above facts it is hoped that the use of mixtures of the alkaloids will enable the treatment to be extended among the masses, as these mixtures are likely to be less

Hick and Diwan Chand (1935) performed experiments in India with two types of totaquina. The trial was carried out on the lines suggested by the Health Committee. More than 250 patients were treated and if the untreated control group is excluded, there

31, so that and both Cinchona

	Type I per cent	Type II per cent
Quinine	32	19
Quinidine	1	4
Cinchonine	11	20
Cinchonidine	30	26
Amorphous alkaloid	15	19

conditions there was

totaquina in clearing *the* blood *of parasites either in benign or malignant tertian ma*

Cinchona febrifuge it has been pointed out is a mixture of all the cinchona alkaloids of the *C succirubra* bark. Residual alkaloids are a mixture of the alkaloids precipitated from the mother liquor after most of the quinine in the bark of *C ledgeriana has been* extracted To this latter certain proportions of quinine sulphate are added and the mixture is used as a substitute for quinine. Both these products are cheaper than quinine and under the name of cinchona *febrifuge have been used* in the treatment of malaria in India with gratifying results The following mixture is prescribed —

Cinchona febrifuge	10 grains
Citric acid	30 „
Magnesium sulphate	60 „
Peppermint water	1 ounce

One ounce of this mixture is prescribed three times a day 2½ hours after meals, for one week. It has been found quite effective but it is liable to produce nausea and vomiting as the amorphous alkaloids present stick to the mouth. The majority of patients however tolerate it well if it is taken at the right time i e 2½ hours after food.

Derivatives of quinine and cupreine in malaria Henry and Brown (1923) showed that the toxicity of quinine base is greater to the paramœcium than that of its salts. Quinine

to be more effective than quinine, by others less so Cupreine sulphate in doses of 1 gm was fo
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(4) Quinine in other Conditions

Pneumonia

Quinine was used in the treatment of pneumonia over half a century but more effective drugs are now available Quinine finds no place now in practical therapeutics of pneumonia

Common cold and influenza Quinine is often used in the treatment of the common cold It cannot reach the mucous membrane in strengths sufficient to produce antiseptic effects but it probably acts as a sedative

Puerperal septicaemia and other conditions Puerperal septicæmia was treated with 2 grains of quinine every few hours

Exophthalmic goitre Quinine and cinchona alkaloids are useful in this condition because of their vaso-constrictor properties on some vessels and secondly because of their effect

30 minims of extract of ergot

Diseases of the circulatory system Quinine has had the reputation for being a cardiac sedative for a long time Oppolzer considers that along with rest and digitalis it is one

disease

Other conditions In lumbag
In the treatment of sciatica, in
sciatic nerve are recommended
are injected at the point where
lies on the unaffected side with the affected thigh half flexed A point is selected somewhat lateral from the midpoint The needle is pushed in for 3 to 4 inches and when it strikes the nerve a smarting pain is felt down the leg

In the treatment of *varicose veins* intravenous injections of quinine into the local veins are employed. Quinine is given along with ergot to cases of atony of bladder and cases of enlarged prostate who can not be operated upon.

Pruritus ani vulvae and scroti have been treated by infiltration of the skin and subcutaneous tissue with 0.25 to 0.5 per cent quinine urea hydrochloride. Itching is at once

arrested and excoriations rapidly healed One injection may suffice to keep down the condition for months As much as 100 to 200 ccm of the solution may be necessary

Venereal diseases Quinine has been used as a prophylactic against contracting venereal diseases, because of its bactericidal action on the gonococci and spirochetıcidal action It is often combined with calomel and gelatine in a strength of 25 to 15 per cent.

Induction of labour with quinine Quinine has been used for many years as a means of re enforcing uterine contractions, especially when they are not strong Most authorities agree that in therapeutic doses it does not excite the activity of the quiescent gravid uterus and therefore, it cannot be relied on for inducing premature labour If however weak contractions are present they are intensified. The greater the tone and activity of the uterus the more rapid is the action of quinine It is considered by some to be safer and its action more persistent than pituitrin Various methods of giving quinine have been adopted.

Watson's method Castor oi ... 7 p m, enema at 8 p m, quinine ...

... after ½ an ounce of quinine mixture containing ... a simple enema is given Two hours after the enema another dose of the mixture is given this is repeated after 3 hours and then four hours later, making a total of 40 grains of quinine. The percentage of success with this treatment is greater than with pituitrin and the danger is less

Quinine as a contraceptive Quinine has been used as a contraceptive in clinical practice for a long time but during recent years it has been replaced by other drugs

6. Toxic Effects

Quinine is one of the least toxic of the alkaloids, the lethal dose by the mouth in animals being 1 0 gm per kilo body weight Frogs are killed by 1 mgm per gramme by the mouth and by about half this amount given by injection Pigeons are not killed by 3 gm per kilo by mouth although 0 5 gm is fatal when given ... killed by 1 0 to 1 5 gm by mouth, by 0 25 to 0 5 gm intravenously A dose given into the artery of ... complete paralysis of the part supplied by the ... to paralysis of the leucocytes which ... e fatal dose in man is 8 to 15 gm by the mouth ... as 30 gm has been taken without producing death Two to three grammes can be tolerated but 5 gm always produces toxic effects

Toxic effects produced by cinchona alkaloids The amount of quinine required to produce toxic effects varies enorm... different individuals The solubility of the salt of the alkaloid employ... total ... total dose of 40 to 60 grains ... fects in sensitive individuals Repetition of doses of quinine in patients who have suffered from cinchonism is not desirable

The toxic effects produced by quinine can be discussed under the following headings —1 Quinine idiosyncrasy 2 Cinchonism

(1) Quinine Idiosyncrasy

... show very peculiar susceptibilities in regard to quinine ... which

urticarial rashes intolerable itching or bullous eruptions which may be accompanied by fever Other symptoms are dyspnœa fever nausea and vomiting Sometimes there are giddiness and fainting There may be extravasation of blood in the skin and perhaps in the intestines and kidneys occasionally there is severe prostration which disappears by the following day but reappears some weeks later when the dose is repeated. In some cases itching of the skin and vesicular eruptions are produced by contact with quinine solutions Sometimes cinchonine or quinidine does not produce idiosyncrasy in cases in which quinine does so and so either may be substituted Idiosyncrasy may suddenly appear in persons who formerly have taken large doses of quinine without any disagreeable consequences It may also declare itself by occurrence of toxic symptoms after small doses (deafness amblyopia etc) which are usually produced after large doses This idiosyncrasy is not commonly met with in the tropics where large doses such as 20 to 45 grains are given in 24 hours and it appears to be similar to that of potassium iodide in which idiosyncrasy is more commonly seen with small doses than with large ones If the serum of a person suffering from idiosyncrasy to quinine is injected intraperitoneally into a guinea pig the animal s susceptibility to quinine is greatly increased Rarely quinine produces a paradoxical or contrary action producing an enormous rise of temperature accompanied by rigors instead of the expected fall This phenomenon still remains unexplained

Test and desensitisation

In susceptible individuals local application of quinine solution (1 in 10 to 1 in 1 000) to the scarified skin produces a marked reaction which is not given by normal individuals This may be used as a harmless test for quinine idiosyncrasy The skin reactivity may be met with in the case of some lævorotatory alkaloids *e g* cinchonidine ethylhydrocupreine etc. and more rarely in dextrorotatory isomers such as quinidine cinchonine ethyl hydrocupreidine Sensitiveness to quinine is not congenital and does not exist in blood relations

Desensitisation This has been proposed and tried successfully in some cases The patient is given 5 mgm of quinine bisulphate plus 0 5 gm of sodium bicarbonate to start with by the mouth After 1½ hour 0 5 gm of sodium bicarbonate and 0 1 gm of quinine are given The two doses of quinine are repeated daily the desensitising dose being left at 5 mgm and the second dose being increased by 0 1 gm every day Another plan is to give 0 5 to 1 0 ccm of adrenalin by injection followed 20 minutes later by a small dose of quinine such as 0 05 gm Next day the same injection of adrenalin is given but the dose of quinine is increased

(2) Cinchonism

Increased susceptibility

This name is given to the early symptoms chiefly connected with the central nervous system which appear when quinine or other cinchona alkaloids are given in large doses This should be differentiated from idiosyncrasy which is a condition of increased susceptibility and which is brought on by very small doses Some individuals however are much more liable to get cinchonism than others The power of producing cinchonism varies with the different alkaloids cinchonine being the most powerful next comes quinine, then quinidine and lastly cinchonidine The association between the symptoms of intoxication and high concentrations of the alkaloid circulating in blood is very striking When the concentration of quinine in blood reaches 10 mgm per 100 ccm symptoms of poisoning appear The early symptoms are nausea vomiting mental

depression, headache (due to cerebral congestion), ringing in ears, giddiness and disturbed vision (due to selective changes in the vessels of the eye and ear) Minor symptoms may be somewhat diminished by bromide salts

When a toxic dose c ... accompanied by loud ro ... permanent There is ... blindness at first partia ... nausea, diarrhœa vomiting and general muscular weakness occur followed by difficulty ... general paralysis, ... cold sweats are ... rge doses paralyse ... llary centres as a ... very large doses. Quinine also produces skin rashes There may be erythema, urticarial weals swelling of the tongue and face œdema of the eyelids, a scaly condition of the skin and a generalised itching eruption It may also cause hæmorrhage from the nose uterus and kidneys Quinine amblyopia and amaurosis have already been referred to

Quinine interferes with the oxidation of the tissues and this oxygen lack causes a spasm of the retinal artery and leads to the changes associated with quinine poisoning Two stages may be distinguished in the action of the drug, in the first stage the quinine, in its capacity as a general protoplasmic poison, acts directly on the retinal elements and the second stage depends on the spasm of the retinal vessels and it is probably acute in onset

A fact of great clinical interest is that when large quantities of quinine are passed ... Ramsden found that the propor ... he drug exceeded 2 gm by the ... ally or 1 2 gm given intramus- ... excrete very large quantities ... from the urine within a day ... per litre in the urine which is ... administration of quinine does ... the same proportion is excreted ... are more liable to ... Lal (1927) found that the incidence of albu... ment was combined with alkali than when quinine was given alone

Apart from albuminuria produced by quinine, renal changes occur in malaria From ancient times quartan fevers have been recognised to be the cause of nephritis Giglioli (1932) has drawn attention to cases of sub-acute and chronic Bright's disease where symptoms develop with the appearance of the parasites in the blood and disappear on the administration of quinine

(3) Visceral Degeneration

Cornwall (1920) showed degenerative changes in the suprarenals and the kidneys, and increased degeneration of the erythrocytes in the spleen after large doses of quinine in rabbits That quinine has toxic effects on the liver has been experimentally proved Intravenous injections of moderate doses in rabbits produce progressive degeneration of liver cells which increases with the increase of dosage Quinine has a certain amount of hæmolytic effect on the blood cells especially in high concentration It modifies the response to other hæmolytic agents such as acid solutions

Macht and Teagarden (1923) ... nidine are more toxic to rats exposed to sunlight or to a qua... ark. Exposure of quinine solution to ultra violet lig... nder it more toxic to ... and also ...

but ... Cinchonine and cinchonidine in large ... the optic thalami Quinidine has ... Cupreine is about half as toxic as quinine. ...uces salivation hallucination and epileptiform ...ressure

The grave effects of cinchonism are only met with when the dose of quinine is increased beyond 40 to 60 grains a day Such large doses were prescribed at one time by practitioners in India and were often continued for long periods These undoubtedly do harm As a rule a maximum dose of 20-30 grains per day, according to the weight of the patient divided into 3 or 4 doses are quite sufficient in an adult to control the fever Such doses are quite safe and effective and as a rule cause no untoward symptoms There is no particular point in giving very big doses by the mouth as the intravenous and intramuscular method can always be resorted to when there is doubt regarding its absorption from the gut

A form of toxæmia occurs in patients taking large doses of quinine for prolonged periods In the old days patients who had suffered from malarial fever were put on large doses of quinine for per [illegible]
frequently met with T [illegible]

[illegible] were due to the action [illegible] stoppage of the drug [illegible] effects of quinine have been attributed by some to the formation of a body called quinotoxin which is formed by the action of free organic acids on quinine and it is suggested that such conditions arise in the gut It is however found that this substance has a very low toxicity and could not be responsible for these effects

(4) Treatment of Cinchonism

[illegible]

symptoms of cinchonism, and therefore quinine has often been prescribed with hydrobromic acid *Some suggest 7½ grains of peptone (Witte) orally half* an hour before quinine is taken, because of its anti-anaphylactic effect, others recommend use of adrenaline A skin reaction by scarification with 10 per cent solution of quinine sulphate has been described In all cases with toxic manifestations, administration of quinine should be stopped and atebrin or paludrine substituted This enables patients sensitive to quinine to be made fit for service in the tropics

7. Mode of Action of Quinine

Direct effect

[illegible] stains It has been found that quinine does not attack the parasites with equal virulence in all the stages of development The asexual forms as a rule are much more vulnerable the sexual forms of *P falciparum* appears to be hardly touched. The action of cinchona alkaloids controlling attacks of malarial fever is not understood There are many points in connection with directing the attack of these alkaloids upon the most vulnerable stage of the parasite about which we have not sufficient knowledge

The concentrations of quinine in the blood attained after therapeutic doses are not sufficient to kill the malarial parasites by their direct action Other factors therefore must come into play

Concentration in blood

Ramsden, Lipkin and Whitley (1918) found that quinine was present in the blood in a strength of 1 in 100 000, seven hours after administration. In a number of human cases treated with intravenous injections no direct correlation was found to exist between the concentration of quinine in the blood and the disappearance of the parasites. From the blood, a certain amount, varying with the individual, but averaging about 40 per cent of

the total amount administered is eliminated by the kidneys *within three to twenty four hours* Very little passes out in the fæces unless there is diarrhœa The balance is fixed in the tissues more in some than in others It is *apparent from these studies* that quinine makes only a brief stay in the blood circulation and is only present here in minute traces, the blood corpuscles taking up *very little* *Acton and King* (1921) concluded that the distribution of quinine between plasma and corpuscles was about equal The question is of some importance the *malarial parasites* being intracorpuscular

The following *concentrations of* quinine were found in the blood by Acton and King after 15 grains were given on an empty stomach

Interval after administration (hours)	Concentration of quinine in blood	Amount in blood (mgm.)	Per cent of the dose taken
Quinine			
1 — —	1 in 150,000	33	3 3
2 — —	1 in 187,000	27	2.7
3 — —	1 in 225 000	22	2 2
Hydroquinine			
1 — —	1 in 250 000	20	2.0
2 — —	1 in 280 000	18	1.8

[illegible]

tertian infection

Malarial parasites are hæmosporidia and as *far as* is known live only in the red blood cells, they are not found in the plasma—in a free condition or in the cells of the tissues The *only occasion on which they are free is when the mature schizonts rupture* and they attach themselves to fresh erythrocytes It is possible that the cinchona alkaloids may *destroy them in one of the following ways* —

(1) *By making the erythrocytes distasteful for habitation of the parasite in the same* way as *E histolytica* will not ingest emetinised blood cells The merozoites are in this way *prevented from* penetrating the red blood cells and perish because they are deprived of the only food they can live on

(2) By parasiticidal action when the parasite is in the red cells It has been said that the action is most marked on the youngest forms less on the mature forms and very little on the gametocytes The intra-corpuscular forms are not more vulnerable to quinine than the extra corpuscular forms Craig after careful study of the action of quinine on malarial parasites in fresh and stained specimens came to the conclusion that it affects *the parasite* injuriously in all stages in man except just prior to sporulation Some of the recent work, however throws doubt on the parasites being in the red corpuscles there *are some indications that they may* lie on the surface

(3) By the destruction of the merozoites when they are passing from one corpuscle [illegible] not affected by quinine and sporulation occurs but [illegible] (Craig) The [illegible] vulnerable to [illegible] rocyte probably [illegible] ole explanation [illegible] sporulation

(4) Morgenroth (1918) believed that malarial parasites [illegible] enter red blood corpuscles which have been treated with quinine It has been recently shown *that quinine* tends to condense on the surface of solutions or at the interface to such a degree that it forms a rigid film If a tough film were formed on the blood corpuscles this might *protect* them mechanically against the entrance of the parasites

(5) By the formation of potent decomposition products in the body It has been shown in the case of the organic arsenicals that the concentration required *to kill the parasites*

outside the body appears much higher than the concentration which can be conceived to exist in the blood stream. This is attributed to their transformation into more effective compounds in the body In the case of alkaloids like quinine emetine etc, the assumption ears of r in It

operty shows alarial that is

(7) It is quite possible that quinine acts mainly on the young forms in the course of em or before contact with nchona even aralyse them their move the red cells

Although the exact method of action of quinine on malarial plasmodia is still unknown Bourne (1934) has brought forward evidence to show that quinine acts by inhibiting reproduction retarding the asexual cycle and decreasing the number of merozoites The mechanism is thus quite distinct from that of acquired immunity where the parasites are killed without any evidence that the rate of reproduction is inhibited

There is no evidence that the prolonged administration of quinine or plasmochin leads to drug resistance on the part of the plasmodia

The action of cinchona alkaloids on the gametocytes Crescents appear suddenly in the peripheral blood on the 11th day of disease increase to a maximum and then decrease The average duration of a crescent wave is 14 days, but crescents may persist for 66 to 128 days, when there are frequent relapses Crescents are most plentiful in new cases and in relapses and are fewer in number in chronic latent and recrudescent malaria In acute cases of malaria administration of quinine for short periods is said by some to favour the appearance of gametocytes in the peripheral blood Two hypotheses have been advanced to account for this —(1) That the administration of quinine expels the gametocytes from the deep viscera to the peripheral blood and (2) that it creates an environment which favours the development of increased numbers of gametocytes According to others quinine in the early stages does not increase but tends to inhibit crescent production

Gametes in blood

Every division of parasites produces new gametocytes the number of the latter increases progressively in the body as a result of repeated attacks The sooner malaria is treated with quinine and the bouts of fever are reduced, the less the number of cycles that a parasite will undergo thus indirectly reducing the number of gametocytes

t produc maximum casionally When the

The cinchona alkaloids have been shown to have little or no action on the gametocytes of malignant tertian parasites in the blood and only slight action on

Effect of quinine

those of benign tertian Administration of *quinine however in doses of 20 to* 30 grains a day reduces the number of crescents probably by cutting off the source of supply by killing the asexual forms According to James (1924) the development of gametocytes in all three species is not morphologically affected by quinine The life of a red cell is said to be 30 days though estimates vary considerably, it follows therefore that crescents cannot live longer unless the dead red cells adhere to the crescents Muhlens and Kirchbaum (1923) transmitted subtertian malaria through *A maculipennis* to a fresh case the donor at the time of infecting the mosquito being under the influence of quinine It has also b administration of quinine are viable pe after administration of quinine w and spreading infection although ver On the other hand *although* quinine will *not* cure a benign tertian infection it will emasculate the benign gametocytes so that there is no risk of their passing on to others (Meyer and Wenyon) There is no other drug except plasmochin which has a direct action on the crescents and destroys them Quinine in very low concentration stimulates metabolism and *increases the rate of multiplication of parasites (Acton* and Chopra 1927), but in the dilutions in which it circulates in the blood after therapeutic doses it decreases the rate of multiplication and therefore few merozoites will be formed

Bass (1921) showed that quinine bihydrochloride in concentrations of 1 in 4,000 when incubated f parasites tions made was shown of 1 in 5000 *still produced infection after 12 hours exposure in patients suffering fro* general paralysis of the insane. The blood left for five hours in contact with 1 in 2 500 donor does not e infected from nd rect Once y the action of quinine and this is a point in favour of the paralytic theory of the merozoites Clinicians know that when quinine is administered after sporulation is completed it does not prevent the next attack.

The mechanism of cure of malaria cannot therefore be by quinine acting directly on the parasites Lipkin (1919) suggested that possibly a metabolite of quinine was the active agent It has also been suggested that possibly an antigen from destroyed parasites stimulates immune body production and helps to overcome the infection Taliaferro Krishnan and others have shown that the cells *of the reticulo-endothelial system engulf and destroy the parasites* directly and upon their number and functional efficiency depends the immunity in malaria

Summary of treatment of malaria with cinchona alkaloids

The cinchona alkaloids have no action on the *sporozoites injected by the* (if they exist Although they act indirectly *by destroying the schizonts from* which the gametocytes develop

The cinchona alkaloids are best suited for treatment of malaria when it cannot be carried out under proper medical supervison They are indicated for mass treatment and for treatment in children (under six years) or where there *is history of mental or nervous disease* Patients coming from an endemic area should be given a full course of cinchona alkaloids (10 days at least) after return

Although all the crystalline alkaloids of cinchona bark are effective, quinine is preferred for an acute attack in an adult, quinine sulphate or hydrochloride is [illegible] r as tablets in doses of ten grains twice [illegible] arger doses are unnecessary and in small [illegible] The course should last for 7 to 10 days [illegible] vith alkali treatment If relapses occurs the course should be repeated each time. Instead of quinine tota-quinine may be used

In pernicious malaria quinine in doses of 7 to 10 grains is given immediately by the intravenous route One to three such injections will suffice to control symptoms and after that quinine is given by the intramuscular or oral route

For chemoprophylaxis six grains daily are advised throughout the stay in a hyper endemic area and for at least ten days after return if not longer

Quinine should be preferably used by the oral route The parenteral routes should only be used if oral administration is not possible

8 Preparations of Cinchona Alkaloids and its Derivatives

Cinchona Bark dose 5 to 15 grains *Extract cinchona* (contains 10 per cent total alkaloids) dose 2 to 8 grains *Extract cinchona liquid* (contains ¾ gr of the alkaloids in 15 minims) Dose 5 to 15 minims *Compound tincture of cinchona* (contains 0.5 per cent of total alkaloids) dose ½ to 1 drachm (2 to 4 ccm) *Cinchona febrifuge* is a mixture of the total alkaloids of cinchona bark of varying composition It has been extensively used in India for the last 50 years with satisfactory results It is cheap and suitable for mass treatment It has recentlly been standardised by the Malaria Commission of the League of Nations

Totaquina A mixture of the alkaloids from the bark of *Cinchona succirubra* and other species of cinchona It contains not less than 70 per cent of crystallisable cinchona alkaloids, of which not less than 1/5th is quinine Dose 1 to 10 grains

CINCHONA ALKALOIDS AND THEIR PREPARATIONS

A Crystalline alkaloids

Quinine hydrobromide occurs in white acicular crystals soluble 1 in 40 of water and contains 76 6 per cent of quinine It is said to lessen cinchonism and is valuable in acute rheumatism Dose 5 to 15 gr *Quinine bihydrobromide* contains 60 per cent of quinine soluble 1 in 7 of water and is suitable for subcutaneous and intravenous injections It is non irritating and the additional hydrobromic radicle tends to prevent cinchonism Dose 5 to 10 grains

Quinine hydrochloride contains 81 7 per cent of base Solubility 1 in 32 of water and in 1 in 2 of 90 per cent alcohol used for subcutaneous injections Dose 1 to 10 gr It is mixed with theobroma oil and forms a part of many contraceptive preparations Quinine hydrochloride is contained in *Tincture quinine* the dose of which is ½ to 1 drachm and *Vinum quininae* dose ½ to 1 ounce.

[illegible]

1 per cent produces local anæsthesia when injected for painting on mucous membrane 10 per cent solution is the best Sterules of various sizes are on the market

Quinine hydrochloro carbamide or urea quinine occurs in small prisms solubility 1 in 1 of water contains 59 2 per cent of quinine. Dose 5 to 15 gr Used to produce local anæsthesia in 1 to 3 per cent solutions, anæsthesia persists from 4 to 6 hours to several days

Quinine phosphate contains 72.8 per cent of quinine base. Dose 1 to 6 gr

Quinine salicylate occurs in white crystals, sparingly soluble in water contains 68.8 per cent of quinine base Useful in sore throat.

Quinine acetyl salicylate contains 64.3 per cent of quinine It is a useful antipyretic and antiseptic compound. *Dose 1 to 5 gr It is prescribed in painful sore throat.*

Quinine sulphate contains 73.5 per cent of quinine base Dose 1 to 15 gr It occurs in white crystals solubility 1 in 800 *of water It occurs in a number of preparations. Ammoniated tincture of quinine* is a solution in 60 per cent alcohol to which ammonia is added, the precipitate formed is suspended in tragacanth. *Quinine bisulphate* Dose *1 to 10 gr*

Quinine tannate contains 30 to 35 per cent of quinine base. It is tasteless and is recommended for children Absorption is uncertain. *It splits up slowly in the intestine* and is therefore not prompt in its action Dose 1½ to 15 gr

Quinine ethylcarbonate or euq [illegible] melting point not below 95°C It is sparingly solu[illegible] easily soluble in alcohol It is pra[illegible] to 5 grains of quinine sulphate [illegible] injection Dose 3 to 16 grains

Aristo quinine or *aristochin* is insoluble in water and is tasteless. It contains 96.1 per cent of quinine Dose 1 to 10 gr It has been used against malaria, influenza, and in small doses in pertussis

Soloquinine is the name given to quinine salicylic ester

Chenophenin is phenetidin-quinine-carbonic ester Both these compounds exhibit the action of both the *constituents of the drug Collobiase of Quinine* is a preparation in which quinine is kept in a colloidal state in combination with arabinic acid. It contains 30 per cent of quinine base It can be given intravenously and subcutaneously

Collosol quinine or the alkaloid in colloidal condition has been introduced.

Tests for quinine

1 *Fluorescence* The alkaloid is dissolved in dilute sulphuric acetic or tartaric acid (the test tubes should be made of transparent glass or silica) One mgm of quinine can *easily be detected in 4 ccm of solution Fluorescence is visible in acid solution* containing 1 in 200000 of quinine The fluorescence may be masked by the presence of chlorides and hence the test is not a very useful one

2 *Thalleioquin reaction* To 10 ccm of the solution of quinine add 3 ccm of chlorine [illegible] ccm of saturated bromine water Shake well and then add one drop of [illegible] alkaline If the propor[illegible] [illegible]cipitated. In more dilute [illegible]inine solution is detected [illegible]can be detected in a still higher dilution [illegible] alkaloids and [illegible] also give this te[illegible] tion products

3 *Tanret Mayer Test* The reagent is prepared by dissolving 1.45 gm of $HgCl_2$ in 80 ccm of distilled water and 5 gm of KI in 20 ccm of distilled water and mixing them [illegible] poured into the KI solution agitatin[illegible] [illegible]loids [illegible]ified [illegible]tube [illegible]loid [illegible]king [illegible]acial 50 ccm of urine and add [illegible] *acetic acid 25 ccm water to 100 ccm*) mix thoroughly and add 25 ccm of saturated aqueous solution of ammonium sulphate, filter till a clear lead free filtrate is obtained Receive a drop of filtrate on a paper moistened with a sulphide to test for lead and also boil to test for albumin *To 10 ccm of* this add 0.5 ccm of Mayer's reagent An opalescence or turbidity indicates the presence of quinine Very slight traces of quinine may only show after the mixture has stood for 10 to 15 minutes

[illegible] as obtained [illegible]d A cloud [illegible] *A precipitate*

due to albumin increases on heating and falls on standing The test responds to 3 grains of quinine taken an hour before examination

Quinine mixtures used in dispensaries in this country are not infrequently below strength Two methods for testing the approximate quantity have been described

(1) *Megaw, Ghosh and Chatterjee method*

Requirements —(1) A supply of long narrow test tubes of equal calibre (5 to 7 mm diameter if possible) Wider tubes may be used but they would necessitate the use of larger amounts of the solutions Calibrated and graduated tubes such as centrifuge tubes are preferable if available

(2) Reagent —Twenty gm of Merck's pure phosphotungstic acid is dissolved in 100 ccm of 12 5 per cent sulphuric acid The dilute H_2SO_4 is made by mixing 5 ccm of B P concentrated sulphuric acid of 1.84 specific gravity with 50 ccm water, cooling, and making up to 70 ccm with more water

(3) The stock solution which is to be tested (This should be diluted if it contains more than 20 grains of the alkaloid in each ounce, in this case the control solution should be diluted in the same proportion)

Method —In one tube take 1 ccm (or one part) of the stock solution in another tube take exactly the same amount of the freshly prepared solution (a third tube may be used for the solution made from alkaloids of known purity) Measurement by a pipette is desirable but with reasonable care equal quantities can be measured

To each of the tubes add 2 ccm (or 2 parts) of the reagent and 1 ccm (or 1 part) of water Mix thoroughly by rolling the tubes between the hands for about a minute keeping them in a vertical position. Do not stir or shake the solutions Allow the precipitates to settle for 2 or 3 hours and compare their heights Any great variations will indicate the necessity for an accurate quantitative examination of the stock mixture

If centrifuge tubes and a centrifuge are available the examination can be completed in a few minutes but the test has been specially worked out so that it can easily be carried out with the simplest possible equipment

The test solution ready made can be obtained from any reliable chemist by supplying

Quinidine This isomeride of quinine is contained in small quantities in most cinchona barks but especially in *C pitayensis C amygdalifolia* and *C calisaya*

Properties Quinidine is alkaline in solution and behaves as diacidic base forming two series of salts The neutral and acid sulphates are soluble in water The acid hydrochloride is sparingly soluble The melting point of the base is 171 5°C and the optical rotation is +236 7° in 97 per cent alcohol

Tests It is fluorescent in dilute sulphuric acid and gives the thalleioquin test. It differs from quinine in being dextrorotatory possessing a sparingly soluble hydriodide (1 in 1250 at 12°C) and a neutral sulphate fairly soluble The tartrate is soluble and this fact is utilised in the separation of cinchonidine

Dose It has a much more powerful action on the heart than quinine, 5 to 7½ grains is the usual dose given two or three times a day orally

Hydroquinidine is the hydrocompound of quinidine and occurs in commercial quinidine

Cupreae cortex or *Cuprea bark* is obtained from *Remijia pedunculata* and other species It contains quinine and an allied alkaloid, cupreine A number of derivatives of the aliphatic series have also been prepared It will therefore be useful to mention some of these preparations in this connection

Methyl hydrocupreine hydrochloride is also known as hydroquinine hydrochloride Dose 4 to 12 gr (0 25 to 0 8 gm) for adults in malaria. In whooping cough in children it is given in 1 to 5 or 6 gr intramuscularly according to age

Ethyl hydrocupreine or *optochin* is a white amorphous powder with a bitter taste, almost insoluble in water soluble in alcohol *ether chloroform* and dilute acids Dose 3 to 4 gr (0 2 to 0 25 gm) *Ethyl hydrocupreine hydrochloride* is given in the same dose as the base and it is soluble in water

Iso amyl hydrocupreine This derivative according to Dixon (1920) is 10 to 20 times more powerful than quinine *in the destruction* of protozoa 0 1 per cent solution acts as a germicide and as a local anæsthetic

Iso octyl hydrocupreine or *vuzin* is said to have a specific action on *C diphtheria* and enough can be given in medicinal doses to clear this organism from the blood

9. Plasmoquine (Plasmochin, Pamaquin)

Plasmoquine is a quinoline derivative known as pamaquin or præquin, British, *rhodoquine* French is an aminoquinoline derivative of methylene blue

Owing to the high price of quinine its bitter taste and its failure to remove crescents from the blood attempts were made to find stronger and better drugs These researches led to the *synthesis of various antipyretic* drugs such as antipyrin (1884) phenacetin (1886) etc. In 1926 Professor Schulemann and his colleagues chose methylene blue which had been shown to have anti malarial *properties as the starting* point for investigation and they prepared a large number of compounds One of these 6-methoxy-8 N 4 diethylaminoiso pentylaminoquinoline *tested by Roehl* was found to be particularly effective against bird malaria. Plasmoquine although orginally derived from methylene blue has a constitutional formula which has analogies to that of quinine Its chemotherapeutic index *is 1 33 as compared with 1.4* for quinine The first announcement concerning it was made in September 1926 It has also been called plasmochin' and later in English speaking *countries it* was called plasmoquin or plasmoquine 'Beprochin is a substance of a similar nature Fourneau 664 is another compound allied to plasmoquine It had been shown that apart from arsenicals the substances effective against malaria in man are effective against bird malaria also This process was reversed in the case of this drug and it was found *that* a drug useful in bird malaria was found to be beneficial in malaria in man Roehl found that plasmoquine had a definite destructive action on the plasmodium in the birds and was nearly 60 times stronger and more effective than quinine One ccm of 1 in 50 000 solution of plasmoquine given daily for 6 days delays development of plasmodium in canaries while the same quantity of 1 in 800 solution will be necessary in man Later it was found that *Haemoproteus* may be temporarily removed from the peripheral blood of thrushes in pigeons plasmoqu ne removes the gametes of *Hæmoproteus* from the peripheral blood stream though they return again after a few days Plasmoquine destroys the gametocytes but not the schizont

(1) Pharmacological Action

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Eichholtz (19-7) studied the action of this drug on the circulation In cats, doses of 2 5 to 5 mgm per kilo of body weight caused formation of methaemoglobin In cats dogs and rabbits intravenous injections produced cardiac incoordination In large doses (1 to 3 mgm per kilo of the body weight) the drug increases the refractory period of the ventricles and heart block may be produced The heart becomes irregular there may be duplication or suppression of the systole With higher doses the heart is depressed and the blood pressure f ... with plasmoquin and ... t decrease the number o ... duced in man Quinine ir ... heart and that

Chopra and his co workers (1933) have shown that plasmoquin in therapeutic doses has no action on the uterus In large doses it produces contractions of the isolated uteri of cats and guinea pigs That plasmoquin prevents the stimulant effect of quinine on the uterine contract ons is not borne out by experiments When proportionally equal doses are employed the action of plasmoquin in the cat and man is similar *Uterus*

Plasmoquin is toxic to the central nervous system

The fate of plasmoquin in the body is not known That it is partially excreted in the urine there is l ttle doubt Its presence can be actually detected in the urine *Excretion*

Nandi & Dikshit (1938) have evolved a test for detecting the presence of plasmoquin *Test for plasmochin in body fluids*

The lethal dose in rabbits is 3 to 5 mgm per kilo body weight intravenously 20 mgm subcutaneously and 225 mgm by the mouth In the cat it is more toxic 5 mgm per kilo intravenously is fatal while t
75 mgm is fatal by the m
doses Death occurs with s
with methaemoglobinaemia.
the blood of the sheep ox
of the oxygen capacity of
acute poisoning the symptoms appear in the following order First there is paralysis of the vasomotor system with fall of blood pressure slowing and then complete cessation of respiration the cardiac rhythm remains undisturbed till the end. Lethal and therapeutic doses in man are not widely separated *Toxicity*

(2) Effectiveness Against Malaria

The drug was first tried on man by Sioli (1926) who cured several patients artificially infected with malaria in the course of treatment for general paralysis Muhlens and Fisher (1927) tried the drug in patients suffering from malaria In a series of 172 cases they found that 0 08 to 0 1 gm per day was an effective dose in tertian and quartan malaria Such doses however produce toxic effects The drug was later tried in most of the malarious countries in Europe the main results of these observations being that plasmoquin in doses of 0 06 gm per day given daily for one week and for 3 days in the week for the next five weeks was effective in curing malaria This was the method recommended by the manufacturers Sinton (1928) gave the drug daily for 28 consecutive days and found this method more effective though more toxic The conclusions arrived at were that the destructive action of plasmoquin is restricted to infections by *P vivax* (benign tertian) in all phases, and that while it has no action on the schizonts of *P falciparum* (malignant tertian) it has a definite action on the crescentic gametocytes of this organism. Plasmoquine is perhaps the only one of the older drugs which has some action on the extra erythrocytic phase

Both benign tertian and quartan paras tes disappear from the blood more rapidly than the sub-tertian and cure is said to be more read ly effected in these infections than with quinine After doses of 0.01 gm 4 or 5 times a day or 0.06 gm daily the fever usually d sappears from the first to the third day of treatment. The parasites may d sappear as early as on the 2nd day or as late as on the 7th day of treatment. Sinton (1928) found that 30 per cent of patients suffering from benign tertian infect ons relapsed after inter mittent treatment with plasmoquin and 23 per cent relapsed after ord nary treatment with quinine Immediate results obtained in acute attacks after treatment with this drug were however no better than those obtained with cinchona alkaloids In quartan fever similar results were obtained but the parasites remained somewhat longer in the peripheral blood. Although the number of cases was small, no relapses were reported in quartan fever Plasmoquin and quinine together are bel eved by many authorities to be more effective in destroying the *sexual* forms of benign tertian and quartan parasites, than quinine alone. *B T and quartan infections*

ms As regards *subtertian infections* plasmoquin has no action at all upon the schizogony cycle and the parasites multiply unchecked. On the other hand it has the unique and remarkable property of *completely destroying* the gametocytes or 'crescents'—a property which is not possessed by either quinine or atebrin. This effect on the crescents can be studied microscopically, *on the first day after plasmoquin* administration the crescents are seen to be degenerated and stain badly, on the second day they are so degenerated as to be hardly *recognisable on the third* day none are found. None of the cinchona alkaloids have any effect on the crescents nor do the arsenicals or the aniline dyes affect them adversely but even small doses (*0 02 to 0 04 gm*) *of plasmoquin* daily for three days are said to render the peripheral blood non infective to anopheline mosquitoes a single dose may ren . . . The de . . .
ing action is said t
These facts are of .
from one person to
infection holds out a hope for eradicating malaria by mass treatment *Mollow* (1928) described the direct toxic effect of the drug on the crescents and the changes which take place in these bodies Definite signs of degeneration were noted in crescents within 36 hours of the commencement of plasmoquin medication and 24 hours later the crescents were entirely disintegrated According to Fischer and Weise (1927) the daily dose of the drug to remove the crescents from the blood is 0 02 to 0 03 gm (1/3 to ½ gr)

Practical trials of antigametocyte action of plasmoquin have been made by Clemesha (1933) Although the trials were on a small scale the results show that it is possible to . . . Two doses of quino-plasmoquine . . . hozoites or schizonts) in the . . . *gametocytes are never found* . . . cted upon by plasmoquin than . . . *e the attack, even of malignant* . . . ure is the trouble and expense . . . severe outbreak of malaria

The maximum dosage without producing toxic effects is 0 03 to 0 04 gm per day in Indian patients According to Muhlens the dosage for quartan and tertian *malaria is 6* plasmoquin compound tablets daily each containing 0 01 gm of plasmoquin and 0 125 gm of quinine divided into 2 or 3 doses This means 0 06 gm of plasmoquin and *0 75 gm of quinine per day, 0 02 gm may be given* 3 times a day for a week The fever disappears in 1 to 2 days and the parasites in 5 or 6 days The amount of quinine to be given daily in combination with . . . In chronic cases with acute symptoms . . . be necessary to give larger doses In . . . ion not more than 0 04 gm of plasmo quin . . . not exceeding six days The patient usually does not develop tolerance to the drug For therapeutic purposes the Fourth General Report League of Nations (1937) recommends for adults a daily dose of 0 01 to 0 03 gm associated with quinine or atebrin given either simultaneously or after a lapse of time Even with such small doses when given simultaneously with atebrin toxic reaction may occur

Children tolerate plasmoquin very well and it has the advantage of being *tasteless, the maximum dose in children up to 6 months of age* is 0 0025 gm three times a day, 6 months to 2 years 0 005 gm 2 to 4 years 0 0075 gm 4 to 8 years 0 01 gm 10 to 15 years 0 02 gm

The dose is varied according to the physical condition of the child giving about 0 001 gm per kilo body weight Intramuscular injections using the same doses are *required in exceptional cases only* Intravenous injections should be strictly avoided The drug should never be given without medical supervision The after treatment can be varied according to the *desire of the physician*

Plasmoquin in pregnancy In therapeutic doses plasmoquin has no effect on the uterine contractions and it is considered to be safer than quinine in malaria in pregnancy

Plasmoquine compound —The insufficient action of plasmoquine on the ring forms and schizonts of subtertian malaria led to the use of a combination of plasmoquine and quinine

combined with plasmoquine

In subtertian malaria treated with plasmoquine compound the fever usually disappears after 2 to 3 days and the parasites between the 2nd and the 7th day Relapses do occur but they are not so frequent as with quinine alone

Quinoplasmine or chinoplasmine is a combination with larger proportion of quinine than in plasmoquine compound Each tablet contains 0·01 gm plasmoquine and 0·3 gm (4½ gr) quinine the dose is three tablets daily for adults

Certain strains appear to be resistant to plasmoquine since in some areas only a few relapses occured after treatment with 0·03 gm of plasmoquine and 15 grains of quinine Yet in other areas same treatment was followed by 50 per cent relapses (Malaria Commission of Holland 1932)

are minimised

(3) Toxicity and Prophylactic Value

Toxic effects

Even
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appe the
treat arly
liable to suffer Cyanosis and epigastric pains were observed very early after trials in man and they are universally present though they vary a great deal in their intensity in different individuals Slight jaundice cyanosis and abdominal pains are by no means rare The appearance of cyanosis ought to serve as a warning to reduce the dose or to stop the drug Cyanosis has appeared after 0·08 gm In mild cases there may only be cyanosis of the fingers nails toes ears and tongue the face and the whole body may be involved According to some it rapidly disappears on subsequent treatment with quinine plasmoquine and quinine being mutually antagonistic in this respect Abdominal pains and gastric disturbances are common when the drug is given on an empty stomach in large doses Some believe they are due to rapid decrease in the size of the spleen It is stated that these pains do not appear if the drug is given after meals

Others have reported sudden attacks of pain which became very alarming and in many cases a course of treatment cannot be finished without toxic symptoms Daily doses of 0·04 to 0·06 gm or even of 0·02 gm if prolonged for ten days may produce toxic symptoms

Toxic symptoms as a rule have not been recorded unless the dose reaches 0·18 gm The face is livid grey but there is no dyspnoea nor undue distress The patient complains of headache, dizziness generalised urticaria trembling curious clammy sweats abdominal pains, vomiting and a sensation of bruising

over the lower ribs The pain may be specially marked in the region of the liver and central necrosis of liver lobules has been observed In some cases the symptoms resemble an attack of cholera —subnormal temperature vomiting diarrhœa and cyanosis being present Cyanosis may be associated with hæmoglobinuria involvement of the liver and intestinal symptoms

The kidneys may show evidence of acute hæmorrhagic nephritis and the liver *of parenchymatous necrosis such as is associated with the quinoline nucleus in* such other compounds as cincophen *The blood turns chocolate coloured and* methaemoglobinaemia and methaemoglobinuria occur Urobilinogen appears in *the urine simultaneously with the administration of the drug and persists for* several days The patient turns drowsy and becomes comatose Pallor with a marked drop of erythrocytes [illegible] ellownes *of the skin are some of the* [illegible] *cent the* leucocyte count rises to 24 00 [illegible] blood is decreased Methaemoglobin may appear in the urine 24 hours after cyanosis and may be accompanied by albumin and casts The picture resembled that of mild blackwater fever Jaundice may occur Cyanosis may last for 24 hours after the drug is stopped but rarely may last as long as seven days The serum becomes brownish with a strong direct bilirubin reaction and with urobilin strongly positive There is a good deal of destruction of red corpuscles the number falling to half the normal amount

Many explanations have been given for the occurrence of cyanosis It has been said to be due to disturbance of the heart rhythm but most authorities believe it to be due to the formation of methaemoglobin which has been detected in the urine and in the serum

It is more likely to occur in patients with chronic constipation In vitro plasmoquine mixed with 1 in 50 000 of blood produces methaemoglobin

[illegible] between the amount of the drug given and the quantita [illegible]

A direct haemolytic effect on the part of this drug is disclaimed and it is believed that it acts on the reticulo endothelial cells (Kupfer s star cells) of the liver whereby its detoxicating properties are decreased

On account of the frequency of toxic symptoms which are sometimes of an alarming nature plasmoquin should only be used under hospital conditions The drug is not as suitable for mass treatment as is quinine.

Prevention and treatment of toxic effects The poisoning can be prevented by careful dosage taking into con [illegible] condition of the patient A few drachms c [illegible] form may prevent the onset of [illegible] hour and a half after a light m [illegible] symptoms have supervened the drug should be stopped [illegible] tly confined to bed and given copious *alkaline drinks* *Stimulants* and mild non irritating diuretics are indicated In severe cases of methaemoglobinaemia and methaemoglobinuria the patient may be benefited by transfusion of blood

Use in epidemics

Prophylactic value Owing to the action of plasmoquine on the gametocytes, the question of its utility in malaria epidemics is worth considering Experiments carried out in Java showed that plasmoquine had a well marked prophylactic value, especially in benign tertian malaria

Mode of action.

Mode of action of plasmoquine The exact manner in which plasmoquine produces its destructive action on the malarial parasites is not understood It has been suggested that [illegible]

There is evidence to show that substances such as glucose which play a part in cell respiration increase the action of plasmoquine on the other hand the action of quinine is unaltered by the addition of such respiratory metabolic products

Haemoglobin

Plasmoquine in blackwater fever – The question whether plasmoquine is liable to induce blackwater fever is as yet unsettled The observations of Amy and Boyd (1936) in India suggest that in certain regions it may be responsible for an increase in the number of patients with hæmoglobinuria It is possible also that prolonged use of plasmoquine may interfere with the new formation of hæmoglobin

Summary.

Conclusions —Plasmoquine is a toxic drug and the hope that it will replace the cinchona alkaloids in the treatment of malarial fever has not been fulfilled On account of its toxic effects it has to be given under strict medical supervision The action in rendering gametocytes non infective to mosquitoes is of very great importance, and with plasmoquine compound there is possibility of sterilising the carriers For the treatment of benign tertian infections the combination with quinine (plasmoquin compound) may be suitable as it is found that a smaller dose is quite sufficient if supplemented with quinine. Although it acts on the asexual phase of benign tertian and quartan forms of malaria, it has no effect on the asexual cycle in malignant tertian malaria For this reason and on account of its toxicity this drug should not be used in the treatment of malarial paroxysms Its chief use is to destroy gametocyte of malignant tertian when they are present in the blood For this purpose such small doses as 0 01 gm twice daily for 2 or 3 days are quite effective. Such doses do not as a rule, produce toxic effects and according to some as much as 0 06 gm daily may be given without untowards effect

Cilional

Cilional was introduced by Schulemann and belongs to the plasmochin series of preparations, its action on gametocytes of *Plasmodium falciparum* was claimed to be as potent as that of plasmochin in doses far less than any that produced toxic symptoms A total dosage of 0.35 to 0.4 gm of cilional administered in doses of 0 03 gm three times a day, is usually sufficient to [illegible]

plasmochin is prefe[illegible] doses of the former drug effect eradication of crescents in a comparatively shorter time, further plasmochin is cheaper than cilional

Certuna.

Certuna is dialkylamino-oxyquinolamino butane and is also said to possess gametocidal properties very similar to plasmoquine The dosage recommended is 0 01 to 0 02 gm thrice daily for 3 to 5 days It can be used in combination with atebrin.

Preparations

Plasmoquine is issued in tablets in three varieties —

Plasmoquine simplex 0.01 and 0 02 gm Dose 1 to 3 tablets daily

Plasmoquine compound containing plasmoquine 0.01 gm and quinine 0 125 gm

Quinoplasmine or quino plasmoquin containing plasmoquine 0 01 gm and quinine 0.3 gm.

Preparations —Pamaquin B P is a yellow to orange powder odourless taste bitter Insoluble in water Dose 10 to 20 mgm or 1/6 to 1/3 gr

10. Mepacrine (Atebrin)

This product was first called 'Erion' or plasmoquin E or Atabrine in USA, is the dihydrochloride of 2 chloro 5-(diethylamino methylbutylamino) 7 methoxyacridine Quinacrine hydrochloride is the USP equivalent It differs from plasmoquine only in the nucleus structure which is 2 chloro methoxy acridine in case of atebrin and 6-methoxy-quinoline in case of plasmochin The side chain is same in both Compounds of similar composition have been produced in different countries and named differently *e g*, quinacrine a French product crinorin an Italian product and acriquine, a Soviet Republics product are all similar as regards chemical constitutional formula

Atebrin is a yellow powder having a bitter taste Its solubility which is only 2 or 3 per cent at room temperature increases to 7 per cent at 40°C Like quinine it is flourescent Atebrin when dissolved in water hydrolyses slowly into freely soluble and sparingly soluble compound so that atebrin in solution is unstable

(1) Pharmacology

Administered by the mouth atebrin is quickly absorbed from the small intestines and passes into the blood stream whence it is slowly excreted unchanged by the kidneys and the biliary tract Beyond a slight irritant action on the gastric mucosa there are no effects referable to the gastro intestinal canal It is fairly well tolerated but when large doses are administered in animals diarrhoea and reflex salivation occur, frequent vomiting is also noticed, the diarrhoea however, usually subsides within 24 hours If the drug is injected intravenously into rabbits under anaesthesia, a fall of blood pressure is obtained within 1 2 minutes This fall is not due to any direct action on the cardiac musculature but is probably due to a transient dilatation of the capillaries in the splanchnic and peripheral areas Slight fall of blood pressure in man has been noted by Ganguli (1933) in a few cases The fall of blood pressure has also been recorded in monkeys following an intravenous injection of atebrin Nacht (1931) also obtained similar results in cats following intravenous injection of 2 mgm per kilo body weight This fall of blood pressure appears to be due to action on vasomotor centres According to Chin (1937) the excised heart of a rabbit is rapidly paralysed by direct toxic action on the heart muscle The plain muscles of the small and large intestines and [illegible] intravenous injections in anaesthetised animal [illegible] pregnant and non pregnant uterus large doses [illegible] the uterus If the liver is poor in glycogen [illegible] the administration of atebrin but this does not happen in normal healthy individuals A slight reduction of temperature ranging up to 1°C has been obtained in rabbits with induced fever This reduction in temperature lasts for about 12 hours

Fate in the body and excretion —Although it may not be possible to detect atebrin in the blood after twenty four hours of its administration it remains in the body for a considerably long period (up to 40 to 60 days) According to some a part of atebrin absorbed from the intestines is accumulated in the liver and spleen The writer's observations on Indian patients confirm the view that there is some tendency towards accumulation of the drug in the body Atebrin undoubtedly persists in the body for a much longer period than quinine or plasmoquine If excretion is hindered there is a tendency for the appearance of the dye in the skin which assumes a yellowish tinge

According to Hecht atebrin is taken up by the organs which it meets first, thus for example if atebrin be administered intravenously it will largely be taken up by the lungs which retain it longest and in case of oral administration the liver will take it up Atebrin is taken up by the liver lungs suprarenals kidney and spleen mainly in that order and then follow stomach [illegible] saliva semen and [illegible] slightly Atebrin is [illegible] muscular injection, [illegible] this is not possible [illegible]

and circulates in the foetal blood Concentration in red blood cells and plasma is the same

Excretion

Atebrin
of a course
possible acc
second day a
up to 15 to 20 days or even longer The excretion is not regular and may stop for a day or two and then reappear The urine is bright yellow in colour The drug is also found in the fæces

Quantitative estimation.

All methods described for the quantitative estimation of atebrin in the urine are based on the same principle In general they all consist of the following steps an immiscible solvent is used for extraction of urine, solvent is then evaporated and the residue thus obtained is dissolved in an acid or instead of evaporating the solvent, the residue is extracted by an acid The colour or flourescence of the resulting solution is then compared with appropriate standards Various modifications have been reported

Toxic effects

In volunteers 0 6 to 1 0 gm of mepacrine produced headache often severe nausea sometime repeated vomiting colicky abdominal pains and diarrhoea and in more severe cases fever and prostration The symptoms began to disappear after 8-9 hours X-ray examination with opaque meal showed increased peristalsis and increased secretion of stomach and colon In persons taking 0 1 gm daily nothing abnormal was observed. Rarely 0.2 gm twice weekly may produce diarrhœa and vomiting

given with 5 mgm of riboflavin (in view of its antagonistic action to mepacrine), 2 pints were given in 4 hours Patient recovered the following morning

Daily administration of 0 1 gm of mepacrine for a period up to 12 months in women
is occured
remained
Mepacrine

Therapeutic index

Chemotherapeutic studies The therapeutic
malaria by
closely app
and assess
the therape
whereas qu
as quinine
atebrin on

Monkey malaria.

Action on the plasmodium The destructive action of atebrin on this plasmodium appears to be powerful Usually two doses of 0 025 gm each given either intramuscularly or intravenously are sufficient to control a very heavy infection which may amount to a million parasites per cmm The drug
plasmodium and all phases c
under its action Even after
and their numbers rapidly
peripheral blood altogether

Owing to its slow excretion atebrin, when given intravenously, appears to exert a more prolonged action than quinine on *P knowlesi* Intravenous injections of quinine are not

effective against a heavy infection with this plasmodium in *M rhesus* unless they are repeated at short intervals say of three or four hours but one injection of atebrin suffices It would *appear that the growth of the parasites* is not checked by quinine probably because of its rapid excretion after intravenous injection

In monkey [illegible] in *M rhesus* infected with *P knowlesi* even after 5 da[illegible] of the drug the parasites invariably reappeared in [illegible] *same rapidity as in the primary attack*, causing death o[illegible] not given The recrudescence could however be checked much more easily than the original attack. One dose as a rule sufficed to control *the multiplication of the parasites though* a *low* grade of infection persisted for a long period After such a dose the parasites appear to loose their virulence and either a scanty infection may persist or the parasites may disappear from the peripheral circulation for long periods without further treatment

(2) Effectiveness in Malaria

The antimalarial efficiency of the drug was first tested by Prof Sioli in syphilitic paralytics artificially infected with benign tertian malaria He administered the preparation to patients on 3 consecutive days and found that 0 1 gm three times a day could effectively control the symptoms and cause a disappearance of the parasites

Chopra and his co workers (1933) tested this drug on the Indian strains of malaria and have come to the following conclusions —

(1) [illegible]
Its destruc[illegible]
and quartan [illegible]
peripheral circulation after 0 6 to 0 9 gm of the drug *i e*, the administration of 3 tablets of 0 1 gm for 2 or 6 days

(2) *The sexual forms or gametocytes are more slowly acted upon than* the asexual forms The gametocytes of the benign tertian and quartan types are destroyed and degenerative changes can be observed in them shortly after the administration of the drug is started The gametocytes of the malignant tertian type *i e* crescents are not affected at all

(3) The drug is effective in doses of 0 1 gm three times a day the course *lasting for five days, making a total of* 1 5 *gm of the drug* for the cure In the majority of patients such a course is effective but in a few of the persistent ones it may have to be repeated after a few days interval The drug can also be effectively given intravenously in doses of 0 1 gm dissolved in 1 to 2 cubic centimetres of distilled water when the number of parasites in the peripheral blood is large

(4) In chronic types of malaria the drug is effective and produces a rapid reduction in the size of the spleen

(5) Atebrin is reported to prevent relapses but the evidence at our disposal shows that this is not the case with Indian strains of malaria Its prophylactic *value is very similar to that of the cinchona alkaloids*

(6) The blood pressure is lowered in some patients during the administration of the drug but in the majority it has no effect The pulse rate and respiration are not markedly affected It has been used in patients suffering from endocarditis and myocarditis without ill effects

(7) The action of atebrin closely resembles that of the cinchona alkaloids

and the introduction of this drug is a distinct advance in the treatment of malarial fevers in India

Action on Sexual forms

... shown that atebrin is not without effect upon ... *P falciparum* used in that country for ... before these forms are detected in the ... al changes in the immature stages of the sexual forms

The effects of atebrin continue for a longer period after the cessation of treatment, the decrease in the percentage of enlarged spleens continues longer and the return of splenic index figures to their former level occurs more slowly than when quinine is employed. The exact effect of atebrin on the process of immunisation requires further study as do the toxic results of prolonged administration There are instances of patients who have taken daily therapeutic doses of atebrin for as long as two and a half years without toxic results Treatment with this drug is believed by some to be less effective in benign tertian and quartan than in subtertian malaria

Relapses

... to prevent ...

a course of atebrin there is ample evidence in experimental malaria in monkeys (*M rhesus*) that the drug does not eradicate infection from the body and that relapses are common In quite a number of these animals after a course of the drug and disappearance of symptoms and parasites from the peripheral circulation the parasites reappeared usually within two weeks and the animal showed symptoms of the disease

Combination with plasmochin

... and others ... cases of benign tertian malaria the com ... judged ... am In ... relapses ... methods of treatment are of equal value with regard to reduction in the size of the spleen The combination of the two drugs is more toxic than is atebrin alone and is not therefore recommended for ordinary cases The combination has distinct advantages in the treatment of malignant tertian cases especially if crescents are present but has no particular advantages in the treatment of benign tertian and quartan cases The best way is to give the usual course of atebrin and follow it up with 0 01 gm of plasmoquine twice daily for 3 to 5 days

Combination with quinine

Atebrin in combination with quinine 7 to 10 grains daily has been used in severe cases of malignant tertian malaria The symptoms are said to be more rapidly controlled than when the drugs are given individually and the relapse rate is also less This is doubtful

Comparative action with quinine

The two drugs are equally effective against malaria but the effective concentration in the blood is more rapidly attained in case of quinine than with atebrin its (quinine's) duration is shorter on account of its oxidation in tissues and rapid excretion If a large initial dose of atebrin is given the effective concentration in the blood is more quickly reached than with small doses

Dosage Atebrin is usually given by the mouth the tablets (0 1 gm) being taken on a full stomach and washed down with plenty of liquid.

Course of treatment

The average total daily dose for an adult is 0 3 gm taken in three equal amounts Some physicians prefer to give the drug in one dose, especially when

large numbers of patients are being treated very heavy persons over thirteen stone are given a total of 0 4 gm daily in four equal doses

Children even unweaned babies tolerate atebrin well and the following daily doses are recommended

Up to 1 year 0 05 gm (i e ½ tablet) 1 to 4 years 0 1 gm 5 to 8 years 0 2 gm Over 8 years 0 3 gm Atebrin is best taken with milk or water The above mentioned doses are based on very wide experience, however weight and general condition of patients should be taken into account

Regardless of the patients temperature administration of atebrin is begun immediately and continued uninterruptedly for seven days The five days course originally recommended seems too short especially in malignant tertian malaria in which at this point isolated parasites still occasionally appear On the other

seven days

Perenteral routes—(a) *Intravenously* 0 1 gm of atebrin is dissolved in 3 ccm of distilled water and as much as 0 3 gm in 9 ccm of water can be injected generally without untoward effects Only after 0 4 gm had been given are serious symptoms such as collapse observed In cerebral malaria with doses of 0 1 gm to 0.2 gm in comatose cases in Ceylon good result were obtained A proprietary (atebrin dimethane sulphonate) 0 375 gm rin dichlorhydrate (i e ordinary atebrin) h l *intramuscular routes* Atebrin musonate is marketed in ampoules containing the equivalent 0 1 and 0 3 gm of atebrin *and the contents are dissolved in 3 or 9 ccm of distilled water respectively* before administration The dose of the latter in children under 12 year is 1 to 5 ccm and for adults 6 to 9 ccm The drug appears to be effective almost as quickly if administered intramuscularly as by the intravenous route

(*b*) Intramuscular injection is suitable not only in comatose malaria but also in cases with gastrointestinal disturbances and for children It is less painful than quinine *During widespread epidemics this method may be useful for mass* treatment although two injections (after an interval of 24 hours) have given *excellent immediate results the treatment must be continued by the mouth in* order to prevent relapse Though the immediate effects of intramuscular and intravenous routes are rapid the cure is not permanent and relapses are frequent Sterile abscesses may form The parenteral route should not be used when severe anaemia is present In doses of 0 2 gm it has been given in cerebral malaria by the intravenous route but it is believed to be not as effective as quinine

Atebrin is claimed *to have prophylactic properties and has been used for* this purpose with good results It has been continued for months in doses of *0 1 gm daily without producing any untoward effects It has also been combined* with plasmoquine for this purpose 0 1 gm of atebrin and plasmoquine 0 01 gm being given together daily but this has no particular advantage Atebrin however is not a casual prophylactic drug and its value is entirely of suppressive nature

Suppressive action Neither atebrin nor quinine act as true causal prophylactic drugs in malaria but when *atebrin is administered in proper doses it suppresses the*

clinical symptoms and prevents paroxysms Malarial infections are thus held at subclinical levels Such use of the drug is specially valuable for military forces

cause with 0 1 gm daily adequate concentration in the blood is not reached till after the third week and the drug has therefore to be started two weeks before the expected period of exposure The administration of the drug should also be carried on for sometime after leaving the malarial area Usually cases of clinical malaria occur 10 days to three weeks after the drug is stopped In case of intolerance to atebrin quinine in doses of 0 5 gm (7½ grs) daily may be used Another method of chemoprophylaxis is to give 0 2 gm of atebrin twice a week and this has also proved effective in military practice during World War II

iods of 0 to 12 function tests 0 months there r sedimentation rate

The act not upon th anophelines since they a

So far as clinical and mass prophylaxis is concerned there is however evidence that biweekly doses of 0 2 gm of atebrin administered during the whole of the malaria transmission season and even for a few weeks longer exert a definite action on the number of malarial attacks This method was tried on a large scale in the army during World War II with good results and no toxic effects were observed

Direct action

Mode of Action —The evidence which however is not extensive suggests that the action of atebrin on the trophozoites of malaria parasites is direct James (1934) showed that after a single dose of of n the parasites of benign tertian a into the a few have been noted by Chopra and coworkers atebrin on *P Knowlesi* and they also made the important observation that a number of flourescent dyes including atebrin are fixed by the plasmodia of bird malaria.

(3) Toxic Effects

Toxicity

Atebrin unlike plasmoquin is not a very toxic drug Double the usual dose of 0 3 gm per day (i e, 0 6 gm in 24 hours) can be tolerated but larger doses may produce gastro intestinal irritation In spite of the tendency referred to above of accumulation of the drug in the system the writer gave two five day courses of the drug with a few days interval between without producing any toxic effects and with therapeutic benefit. Some patients complained of slight pain or a sensation of uneasiness in the epigastric region soon after taking the drug This generally started on the second or third day and persisted as long as the drug was being administered The pain was never so severe as that produced by plasmoquine In none of the series were the severe abdominal pains described by Green (1932) observed A number of patients complained of headache and loss of appetite while the drug was being given but this also passed off when atebrin was stopped In some of the patients, diarrhoea was produced on the second and third days of treatment and persisted while the drug was

being given The diarrhœa was of a mild type and no particular treatment was necessary It stopped with the cessation of the drug In a few patients especially those who were obese palpitation occurred but it stopped when the drug was discontinued A yellow *staining of the skin and conjunctiva occurred* in several of our patients but the colouration as a rule was very slight and in none of the patients did it amount to a jaundice like appearance It is not true jaundice but merely represents excretion of the drug by the skin Some workers consider that intense pigmentation *of the skin is necessary to produce a cure*

Atebrin pigmentation is most marked on the dorsum of the hands and feet and also on the face and forehead The sclerae are not markedly tinted. Atebrin pigmentation may be mistaken for other conditions which cause mild jaundice such as pernicious anaemia yellow fever, subacute bacterial endocarditis and Addison's Disease The urine should be examined for atebrin for diagnosis Urinary and intestinal excretion should be kept at high level during atebrin treatment Saline purgative should be given and large amounts of fluid should be taken while atebrin is being administered

Mental disturbances have been observed in patients who have received atebrin I [illegible]
ing a feel [illegible]
or transier [illegible]
symptoms accrued It has been suggested that this may be the result of [illegible]tion of malarial toxins which act on the cortical centres Others believe that it represents the *emergence of pre-existing personality defects and not* so much the specific toxic action of the drug

To prevent reactions the atebrin should be taken after the evening meal or with a meal after which there is a long period of physical rest Plenty of sugar or glucose with the meal is also helpful If a patient shows signs of intolerance start with a small dose and then increase gradually

Preparations —

(1) Mepacrine hydrochloride B P is a bright yellow crystalline powder odourless, taste bitter, solubility in about 40 parts of water Dose 0 1 gm or 1½ gr Therapeutic doses—0 2 to 0 5 gm or 3 to 8 gr daily in divided doses in tablet form

(2) Mepacrine methanosulphonate a bright yellow crystalline solid, odour less, taste bitter, soluble in 3 parts of water and 3 parts of alcohol Dose—0 1 to 0 3 gm or 1½ to 5 gr

11. Other Drugs Used in Malaria

Hydroquinine or methylhydrocupreine is obtained by the hydrogenation of quinine A combination *of this compound with an acridine dye and a bile salt has been* introduced under the name of Tebetren which is described as methyl hydrocupreine methyl acridine-dehydrocholate

The bile salt is said to render the compound less toxic Malarcan is a preparation of *similar nature prepared* by an Austrian firm. The drug is available for oral administration in tablets of 3 grains each and in ampoules of 2 1 ccm and 1 1 ccm for pereneral administration

Chopra and his co workers tested malarcan in a series of cases The drug controlled the clinical symptoms of malaria in much the same way as quinine but parasites took longer to disappear and relapses were more common *It has no effect on the sexual forms* of malignant tertian parasites.

The Italian Biochemical Institute, Milan, prepared a drug 'M₂', which, according to the *M₂*
... manganese iodide and of concentrated extract of
... erify the claims put
... s inoculated by the
... is almost absolute
... of *P falciparum* in
... of treatment by this

... copper oxyquinoline sulphonate
is a greenish amorphous
under ordinary conditions
activity against malaria
... m infections, and monkey

Sulphonamide Compounds

For some years sulphonamide derivatives have been the subject of intensive study on *Prontosil* the part of chemists experimental pathologists, and clinicians Prontosil was shown to be effective in the treatment of malaria by de Lein (1937), and Chopra et al found that prontosil in doses of 3 to 4 gm daily for ...

M & B 693

... five day's course of treatment do not
... nt numbers to be detected in thick films

Sulphapyridine sulphathiazole and sulphadiazine are also effective, the action of the last named being the most powerful On account of their toxicity however their use in the treatment of malaria is not recommended

Miscellaneous Drugs used in Malaria

Certain other drugs are believed to have some influence in causing the parasites to disappear from the peripheral blood or perhaps in assisting the patient to resist the invasion of the parasites These drugs can be divided into two groups (1) those which are given in combination with quinine and (2) those which are given by themselves especially where quinine is not tolerated

(1) Drugs used against malaria in combination with quinine

(i) *Preparations of Arsenic, Antimony, Iron, and Mercury*

Arsenic

given in doses of ½ to 1 oz (15 to 30 ccm) Arsenic in inorganic form has been shown to have no action whatever on the malarial parasites

Organic preparations of arsenic are said to have a marked effect on some of the pathogenic protozoa and are believed by some to have a destructive effect on the malarial parasites. *Neo-arsphenamine* is said to abort the symptoms in practically every attack of malarial fever and thus save the patients from getting attacks of fever which are very debilitating The convalescence is shortened and the chances of recovery are enhanced. They also have an excellent tonic value and the patients recover quickly and return to work *Sulph arsphenamine* in doses of 0.3 to 0.5 gm subcutaneously or intramuscularly is also effective

Soamin and *arseno benzol compounds, stovarsol* and *treparsol* have been frequently *Soamin* tried either alone or in combination with quinine One gm of the sodium salt of stovarsol *stovarsol* in 10 ccm of distilled water given *intravenously cleared the blood of P vivax* in seven artificially infected and two naturally infected cases and prevented relapses for two months

The drug acted better on old pigmented parasites the older schizonts and the gametocytes Sinton (1927) treated 25 cases of benign tertian infection with stovarsol giving up to 4 0 gm in 5 days 92 per cent relapsed Stovarsol is said by some to be without effect on the parasites of quartan and malignant tertian fever

ol

When it was found that arsenical preparations in general have only a feeble action on malaria parasites it became the custom to combine these remedies with quinine The mixtures chiefly used are *quinostovarsol* (Fourneau) and *quinine troposan* (May and Baker) On behalf of the Malaria Commission several workers have made clinical trials with quiniostovarsol The general trend of opinion seems to point to the fact that these drugs are not of much use.

d

The view held by some observers that *tartar emetic or other compounds of antimony* have an effect on the malarial parasites has now been abandoned though some of them still hold that they may be useful in preventing relapses

Mercury compounds such as *perchloride mercurophen mercurosol* and *mercurochrome 220* have been tried in the treatment of malaria without success They have no curative action in human or avian malaria

Coal tar preparations The use of medicinal methylene blue (methylthionine hydrochloridum) against malaria was first suggested by Ehrlich and Gullaman. It has been tried by many observers with varying results The preparation used should be free from metallic impurities especially zinc chloride which may cause vesical and rectal irritation The drug is given in doses of 1 to 4 grains (0 06 to 0 25 gm) in cachets or capsules 3 or 4 times a day for a week or more the total daily dose not exceeding one gram It is excreted in the urine which becomes blue and the stools also turn blue on exposure to air In the pernicious type methylene blue has been given combined with quinine intravenously 5 ccm of 1 per cent solution being injected It has been tried in doses of 0 2 gm three times a day at two hour intervals, in the treatment of quartan malaria which does not yield to quinine so readily as the other forms The writer has tried a combination of quinine with methylene blue in quartan infection and considers it superior to many other forms of treatment

Liquid carbolic acid 6 to 12 minims daily for a period varying from 4 to 6 weeks have *been tried in the treatment of* benign tertian malaria but the results are disappointing

Liquor hypochlorous co., which contains approximately 0 07 per cent of hypochlorous acid was tried intravenously in cases of malaria which appeared to be refractory to quinine. Quinine has also been combined with iodine especially in the treatment of chronic malaria.

Quinine does not act efficiently when the liver is not active For this purpose it has been combined with such drugs as calomel rhubarb aloes Warburg's tincture contains aloes rhubarb saffron gentian ginger cinnamon camphor pepper and a number of other things along with quinine sulphate In doses of half an ounce 2 or 3 times a day on an empty stomach it is effective in the treatment of malaria

Organotherapy has been used as an aid to quinine treatment Preparations made from bone marrow and suprarenal gland have been tried Bone marrow extract may be given in the form of tablets 1 to 3 being given daily or as a glycerin extract which is sold under the name of 'marrabain' It has been suggested that low blood pressure in pernicious malaria is due to inefficiency of the adrenal glands and for this reason suprarenal gland extract has been given ıı [illegible] for constrict ing the blood vessels in [illegible] flush them with blood containing qu [illegible] h 0 01 mgm and gradually increased [illegible] negaly As many as 40 injections m [illegible] ated spleen substance has also been used in doses of 3 to 10 grains daily Pluriglandular extract, i.e. a combination of suprarenal spleen pancreas and thyroid has been used on theoretical grounds None of these produced any remarkable effect

Radio therapy has been advocated especially in the splenomegaly of malaria applications being made over the region of the spleen In chronic cases the effect on the spleen is appreciable In acute cases heavy dosage is dangerous Taking into consideration the length of treatment its difficulties and inconvenience it should be rejected in *favour of quinine and* arsenic only

(2) Miscellaneous Drugs used against malaria

A number of medicinal plants have been used in the treat... centuries, but none of them have shown any special effect on... brief description of some of these remedies which have been... methods is given below —

The only reference by the old writers regarding its medici... external application for pains in the chest Vaughan (1921)... tribes of certain parts of Bihar were well acquainted with th... treatment of malarial fever and also of blackwater fever They... leaves, of the root bark or young stems and take it internally... much benefit Preference is given to the dark coloured root p... variety

Vaughan (1921) tried this drug in a series of cases in both... that it gave very satisfactory results Chopra Knowles and ot... the drug and found it has no effect what so ever in malaria

Peganum harmala Two alkaloids named *harmaline* and *ha*... *Peganum harmala* which grows in abundance in Northern Ind... action very similar to quinine In acute malaria the action is no... quinine but harmine is said to have been successful in cases... quinine had failed The writer has tried harmaline in doses of... out any effect

Berberis aristata (Rasaut) which grows on the Nilgiris an... two alkaloids named *oxyacanthine* and *berberine* Both Alstonia... used in India and the eastern colonies in the treatment of mala... advocated berberine as a provocative in latent malaria and consi... megaly The writer tried berberine sulphate in doses of 3 to ... in the treatment of malaria without success

Holarrhena antidysenterica The bark is used in some part... malaria The writer has tried the alkaloid isolated from the ba...

12 The New Antimalarial Drugs

(1) Paludrine

The large amount of chemical synthetic work which had been carried out all over the world following the introduction of pamaquin (plasmochin) and mepacrine (atebrin), had been mainly concerned with derivatives of either acridine or quinoline but no material advance had resulted A number of attempts had been made by various workers to build up anti malarial structures on other heterocyclic ring system such as the phenanthridine benzoquinolines pyrimidoquinoline, quinazoline and carbazole rings but little success attended these efforts. Mepacrine remained the outstanding substitute for quinine With the lapse of time it became increasingly clear that no fresh advance was to be expected unless a completely new lead was obtained and with this end in view investigations were commenced in the research laboratories of Imperial Chemical Industries Ltd at Manchester by *Curd, Davey and Rose*

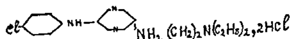
(i) Experimental work

The guiding principle in this work was the fundamental knowledge which emerged from the pioneer researches of Schulemann Schonhofer and Wingler and which led to the synthesis of pamaquin namely that by linking a basic residue of a certain type of an amino group in a heterocyclic ring system such as quinoline acridine etc and in some cases in a non heterocyclic structure such as triphenylmethane anti malarial activity against avian malaria resulted.

The discovery of the anti malarial action of sulphanilamide by Diaz de Leon in 1937 and its confirmation by increasing number of clinical reports led to speculation as to their mode of action As the sulphonamides show no structural resemblance to the other types of known anti malarial compounds it was argued that their activity might be due to the fact they are aniline derivatives of which the pharmacological properties are controlled by the sulphonamide group which promotes absorption from the gastrointestinal tract and the penetration of the erythrocytes which are the habitat of the schizogonic forms of *the malarial parasite* These sulphadiazine and suggested t possess anti malarial properties and take part in a number of that pyrimidine would possess that these would include activ

It is postulated however that in order to produce an effective chemotherapeutic substance

Instead of starting with the simple pyrimidines investigation of derivatives of the anilnopyrimidines was taken up and here anti malarial activity was immediately encountered in the compound 2666 which has the formula



The compound 2666 was first prepared in October 1942 and its biological activity ... established This however was not of a high order and in ... emical constitution led ... nst avian malaria and ... ne its activity in all ... led to the synthesis ... alarial activity 4430 ... was superseded by

4888 or Paludrine This drug was first synthesized in November 1944, and clinical trials first at Manchester and later in Australia established its efficiency in all forms of human malaria

4888 Paludrine

Two important considerations in the life-cycle of malarial parasites helped considerably in the discovery of these new compounds Firstly Schaudinn observed that it has never been confirmed that injected sporozoites penetrate red blood cells directly and secondly there is a period of days or weeks following the bite of a mosquito before parasites can be demonstrated in the blood The immediate fate of the injected sporozoites was until recently uncertain, but it has now been shown that a period of development of the parasite occurs in the tissues of the vertebrate before the red cells are invaded and it is the duration of this *'tissue phase'* which constitutes the incubation period A simple experiment shows that the sporozoite quickly leaves the blood stream and that no blood infection can be demonstrated subsequently for several days Thus if sporozoites of *Plasmodium gallinaceum* are injected intravenously into chicks subinoculation of the injected chicks between a period of 15 minutes and about two days afterwards yields negative results The development phase occurring during this period is the post sporozoite phase or tissue phase The parasites at this time have been called cryptozoites

The tissue phase

Cryptozoites

It ... be apparent that there ...

aimed at the blood phase From this point of view quinine was the great specific in malaria and it was a substitute for quinine that was being searched for in earlier experimental chemotherapy and it was the efficacy of quinine in the experimental infections which formed the index for the utility of synthetic antimalarial drugs Thus it was the blood phase which was used for experimental work and culminated in the development of the Roehl test for anti malarial compounds The search for drugs to kill either the sporozoites or the tissue phase *i e*, a search for *causal prophylactic drugs*, drugs which would prevent parasites ever appearing in the blood was neglected

The Roehl test is based on the fact th ... with *Plasmodium relictum* a period of 4 ...

The Roehl test

... that ... ut the disco ... phase, ...

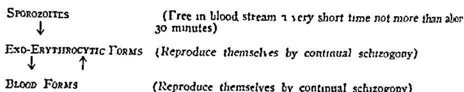
Need for a new method of testing

should also be sensitive to all the other types of drugs known to be efficacious in human malaria. Such infections were discovered in 1938 in the *P gallinaceum* infection of chicks and *P lophurae* in ducks.

P gallinaceum infection in chicks possess the requisite qualities for experimental infection. This organism which was first described by Brumpt in 1935, who obtained his material from wild fowl of Indo China. The parasite is easily maintained in a large, cheap and

P gallinaceum

easily kept laboratory animal Its prominence was achieved through the work of James and Tate (1937) who described a stage in its life-cycle in the chicken which existed in cells other than the red blo
cells in all the tissues of
lungs and kidneys James
might exist in human
erythrocytic forms have
all forms of malaria the sporozoite after inoculation into the vertebrate host, develops first in the tissues and only at the end of this tissue phase does the parasite invade the red blood calls This view may be represented diagrammatically as follows —



The P gallinaceum test in chicks for assessing anti malarial activity—Six days old chicks ith blood drawn from
heavily old The inoculation
should n an acute infection
the pea ie average 300 to 400
out of the contrast between
treated infection might rise
slowly for a day or two but
to rise rapidly and finally reac At
this stage the untreated infectic It
is thus possible to detect even

The time table of the full *P gallinaceum* test as described by Curd Davey and Rose (1944) is as follows —

Monday—(1) 9 a.m Donor chicks with a four day old infection and showing at least half the red cells parasitized are bled The blood is then mixed with an equal amount of citrate heparin mixture and is further diluted with citrated saline *to give a mixture containing approximately 45 million* parasitized red cells in each 0 2 ccm

(2) Selected chicks weighing between 40 and 55 gm are inoculated into right

roups of six. Six birds are used each control group

(4) 4 P M for a 50 gm chick and dissolved or dispersed in 1 ccm of water is administered by a catheter tube passed into the gizzard

Tuesday—Dosing is repeated at 9 a m and 5 p m

Wednesday—At 9 a m all birds are dosed, at 10 a.m smears are made, at 5 p m dosing is repeated

Thursday—Procedure as on Wednesday

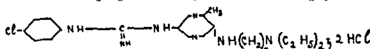
Friday—At 9 a m smears of control birds are made stained and read If the parasite level indicates that the peak has been reached smears are made of all birds They are then stained with Giemsa read and the test ends"

the standard anti malarial drug against which the new drugs activity The dosage of standard drug used was in which for mepacrine is in the region of 2 mgm/50 gm s is the smallest dose which accomplishes practically
everything the drug is cap increasing this dose many times will *not materially* improve the results

The first new anti malarial drug unrelated to any previously known drug discovered was 2666

Its critical dose region was found to be 2 4 mgm/50 gm and its chronic tox city for mice about two and a half to three times that of mepacrine. The drug was tried clinically in human malaria at the Liverpool School of Tropical Medicine but even with the maximum tolerated doses the results were negative However since 2666 was an entirely new type of anti malarial drug there was the possibility of increasing its anti malarial power by further modifications of the nucleus Th s was achieved in 3349 wh ch differs from 2666 in having a guanidine linkage between the two ring systems thus —

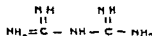
Activity o



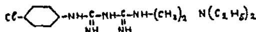
The critical dose region of 3349 and its chronic toxicity figures for mice were in the vicinity of the correspond ng values for mepacrine and its anti malarial activity against *P gallina ei m* was almost as good. On clinical trial against malignant tertian, benign tertian and quartan malaria, in doses of 200 mgm thrice da ly the results were as good as could have been expected with quinine and no toxic reactions were observed

Synthesis of biguanide compound

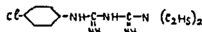
Following the synthesis of 2666 and 3349 Curd, Davey and Rose continued their studies [illegible] ds to their anti malarial activity [illegible] ounds in order to determine at [illegible] compounds were salts of strong [illegible] ad to be retained in subsequent [illegible] 3349 was not originally thought [illegible] omit it If the function of the [illegible] gen atoms suitably orientated to provide the necessary prototropism then the entire—$C(CH_3)=CH$—unit of the pyrimidine ring might also be inessential and it was suggested that the cyclic system could be dispensed with in this portion of the drug molecule With these portions of the molecule omitted 2666 then appeared as a derivative of biguanide



and 3349 as a deriv ative of an extended biguanide Accordingly a b guan de com pound having the formula

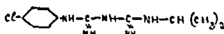


was prepared but the product proved inactive in the chick test However it wa thought that this might be due to the strongly basic properties of this substance This was corrected and resulted in the compound 3936



This substance showed marked ant malarial activity

Further researches on the biguanides resulted in the synthesis in November 1944 by Curd Davey and Rose of 4588 This compound was found to possess the highest degree of anti malarial activity of the whole series of these new compounds and exerted a strong causal prophylactic action 4588 has the formula N_1—p—Chlorophenyl—N_5—isoprop



Biguanide hydrochloride and was named PALUDRINE. It is a colourless crystaline compound freely soluble in water, and melting at 180°C

(ii) Biological results

The following is a brief summary of the results obtained from all the work described above

1 Sporozoites which are the means of transmitting malarial infection from the mosquito to the vertebrate host in all species of *Plasmodium* have been shown in *P gallinaceum* and *P relictum* to undergo a cycle of development in the solid tissues and circumstantial evidence indicates that a similar cycle occurs in all species of malarial parasites The forms which develop directly from the *sporozoites are unpigmented* and are called the primary *i e*, extra erythrocytic forms or cryptozoites Drugs are considered as having a causal prophylactic action if they are active either against the sporozoites or the primary *e e* forms

No known drug has any action on the sporozoites of any species but the sulphonamides are active against the *primary e e forms of P gallinaceum* although not against those of any other species as far is as at present known.

the sulphonamides,
was
cath *lophurae* and *P*
wou ntertained that it
onsiderable extent
justified by results of clinical trials now taking place in all parts of the world

2 At the end of *the period of development of the primary e e forms there is a* release of parasites into the blood stream In chicks this takes place about 36 hours after inoculation of sporozoites In human malaria the earliest times at which parasites have been *recovered from the blood is about 6 days after inoculation of P falciparum* sporozoites and about 8 days after inoculation of sporozoites of *P vivax*

The density of the blood infection gradually increases and at the same time the *e e* forms in the solid tissues also increase in numbers

3 *It is known that none of the standard* anti malarial drugs such as mepacrine and quinine have any apparent action on the cryptozoites (e e forms) and clearly if these are present they may serve as reservoir for the release of blood forms It follows therefore that *a causal prophylactic drug active against e e forms should also achieve radical* cures This point is in process of checking by using sulphadiazine or sulphamezathine and 4888 in a long series of experiments All these substances possess marked casual prophylactic properties in infection of young chicks and since none of them has any action on sporozoites the prophylactic results are due to their action on e e forms If treatment is begun early enough all of them are capable of completely eradicating the infection but *4888 is the only one with which treatment can be delayed until 2 or 3 days* before death is expected and the mortality rate still be influenced The difference between 4888 and the others in its effects on *P gallinaceum* infections is probably one of dynamics of drug action *because all these substances influence the development of e e* forms in infections of young chicks induced by the inoculation of infected blood If such infections in 6-day old chicks are treated for as long as possible with mepacrine and quinine the chicks commence to die after about 14 days and death *is due to blockage of* the brain capillaries with e e forms These infections can however be treated with 4888 or sulphadiazine and death of the chicks prevented It seems that the differences between 4888 and the sulphonamides in their effects on *infections with P gallinaceum* are due to the much more intense and much more rapid action of 4888 on the e e forms

(iii) Extra-Erythrocytic Phase in Human Malaria

Stud ... *h is known to reproduce only in endothelial*
cells sho to demonstrate the presence of schizonts in
the tissu after the infection with sporozoites had taken
... at other times is proved by Brumpt's
after the blood has been
Further evidence of the
afforded by the lack of
taken from birds or human
n fails to produce infection
d birds or human beings
roduced by inoculation of
ntinuously infective This
mum incubation period of
means that as judged by blood ... four days following injection of sporozoites a minimum incubation period which cannot be reduced however great the dose of sporozoites When infected blood is inoculated the incubation period *is progressively reduced* with every increase in dose

As regards the merozoites resulting from the first and subsequent exoerythrocytic schizogonies these vary in their disposition to enter other endothelial cells or the red blood corpuscles In this respect they are "histotropic" or "hæmotropic." In *P relictum*

medite position in this respect

Fairley N H (1947) working with the Medical Research Unit in Australia carried out a large number of subinoculation experiments Viable sporozoites were demonstrated in the circulating blood of volunteers for from half to one hour after inoculation of parasites by the bite of Anopheline mosquitoes This was followed by a period lasting six days in P falciparum and eight days in P Vivax infections during which pre erythrocytic forms are undergoing schizogony in the reticulo endothelial cells and during which time massive subinoculations of blood from heavily infected individuals persistently failed to induce Malaria in recipients It would thus appear highly probable that an exo erythrocytic mechanism occurs in human malaria though this has not yet been conclusively demonstrated This would explain the temporary non infectivity of the blood after injection of sporozoites and would also explain why in naturally acquired malaria a short treatment of an acute attack with quinine or mepacrine although highly effective in clearing the peripheral blood of parasites often fails to prevent a relapse These drugs while highly potent against erythrocytic forms, are presumably inactive against the extra erythrocytic forms and relapses may result from further invasion of the blood by the persisting unaffected exo erythrocytic forms This presumption is further borne out by the observations that artificially induced P Vivax infections by inoculation of blood from infected patients, are readily cured by a short course of treatment and relapses rarely follow, presumably due to absence of exo erthrocytic forms

Evidence adduced from chemotherapeutic experiments suggests that in human malaria, the exo erythrocytic phase in P falciparum infections is a short one lasting only 6 or 7 days and Schizogony Cycles of this phase are few perhaps only two or three after which all the parasites convert into erythrocytic phase Thus treatment of an acute attack of falciparum malaria by drugs acting on the asexual blood forms if continued for three to four weeks usually completely eradicates the infection With P vivax infections, however, evidence suggests that the schizogony cycles in the exo-erythrocytic forms may continue indefinitely and last for several months and treatment however intensive of such infections with anti malarial drugs frequently fails to prevent relapses

The above experiments showed that paludrine and plasmoquine are complete causal prophylactics in P falciparum infections but only partial causal prophylactics of P vivax

Raffaele (1946) claims that he has demonstrated exoerythrocytic stages of development in *all* the three human parasites chiefly in bone marrow taken by sternal puncture from patients a few days after infection by sporozoites Only in the case of *P malariae* has he been able to demonstrate such forms a year after infection had taken place. He notes that the existence of these stages accords an explanation of the failure of various drugs to prevent infection from sporozoites though the drugs are known to be active in the case of the erythrocytic stages of development He shows that the demonstration of the exoerythrocytic forms in human malaria by himself and others establishes, once for all the similarity of the human and avian parasites.

Angelini (1947) in a critical review of the various records of occurrence in smears of the bone marrow and other organs of exo erythrocytic schizonts of human malarial parasites is of the opinion that upto the present no reliable morphological record of these stages in human malaria has been made He finds that detached portions of cytoplasm of cells as occurs commonly in smears of bone marrow may simulate these stages

(iv) Pharmacology & Toxicity of Paludrine

It has not been fully worked out but preliminary experiments have been carried out on its absorption and excretion in volunteers who were given 50 or 500 mgm of the drug every 12 hours for 14 days The drug is absorbed from the gastro-intestinal tract and maximum concentration in the blood is reached on the 4th or 5th day after its commencement The concentration is then maintained more or less The fall away of concentration in plasma is very rapid after the drug is stopped but it can be detected in urine up to nine days after cessation The urinary output roughly follows the same course and drug can be detected in the urine after 12 hours

Paludrine has not been used in the treatment of malaria long enough to enable the clinician to find out its toxic effects From the data collected so far it appears that its toxicity is very low In such large dosage as 1 0 gm daily (three times larger than the effective therapeutic dose) paludrine when administered to volunteers with overt malaria may produce toxic effects which are not serious and which may be relieved by diminishing the daily dose or by cessation of therapy for 1 to 2 days The chief toxic effects observed have been irritation of the gastro intestinal and urinary tracts, vomiting occurs and red blood cells epithelial cells and occasional hyaline or granular casts may be found in the urine

Volunteers taking 500 mgm twice daily for 14 days who carried on their normal work rarely complained of some abdominal discomfort and pain appearing about 30 minutes after a dose most noticeable in the first few days of the course One volunteer vomited after the 5th or 6th dose As much as 700 mgm twice daily can be tolerated provided the patients are kept in bed for first few doses

A transient increase in myelocytes in the peripheral circulation which occurs on the 7th to 10th day after commencing therapy for overt malaria has been frequently observed Whether this reaction can be interpreted as a direct toxic result of drug action or as specific stimulation by the drug of the myeloblastic tissue of the bone marrow recently released from the inhibitory effect of malarial infection is not clear

Chen and Anderson (1947) made the following observations on the toxicity and general pharmacology of paludrine in various laboratory animals After administration of the drug in various doses to rats no pathological lesions could be demonstrated In anaesthetized cats the drug was found to lower the blood pressure and accelerate the respiratory rate The isolated rabbit s uterus and intestine and the isolated guinea pig s intestine are relaxed but the isolated guinea pig s uterus responds by contraction The action on the blood sugar of rabbit is to produce a slight hypoglycaemia

(v) Paludrine in human malaria

(1) A large series of experiments have been performed to determine the anti malarial activity of paludrine both in volunteers infected with strains of *P vivax* and *P falciparum* and natural infections The effective therapeutic range of the drug is wide and in doses ranging from 10 to 700 mgm twice

daily it cured the clinical attacks quickly and effectively The mean time taken for clinical recovery as determined by feeling of well being and fall of temperature to normal and for disappearance of plasmodia from the blood was approximate to that with quinine and mepacrine In dosage of less then 10 mgm twice daily it was not uniformly effective in dealing with the clinical attack This extremely wide therapeutically effective range of dosage is in marked contrast to the limited rage of quinine and mepacrine

2) Paludrine has proved superior to all known anti malarial drugs as in non toxic dosage it is a true causal prophylactic exerting a powerful lethal effect on extra erythrocytic forms of *P falciparum* and fully protecting volunteers receiving viable sporozoites by mosquito-inoculation In *P vivax* sporozoite induced infection it is only a partial causal prophylactic the extra erythrocytic forms are inhibited but eradication does not regularly occur The only other drug which has a similar action is plasmoquine, but this drug has to be given in a dosage which is too dangerous for routine use in man

3) Paludrine in non toxic dosage controls malarial fever and terminates the clinical attack It is a powerful schizonticide both in vivax and falciparum malaria It appears to act on the early schizonts interfering with nuclear (chromatin) division It produces radical cure in malignant tertain malaria 64 out of 65 individuals with sporozoite induced infections being completely cured even by 0 1 gm daily for 14 days The Cairns results suggest however that where individuals are not cured the weekly administration of 1 2 tablets (0 1-0 2 gm) indefinitely would prevent relapses until cure was attained

4) Though not gametocidal in the accepted meaning of the term sterilisation of the infection occurs in mosquitoes fed on M T or B T gametocyte carriers a few hours after taking the drug This sterilization effect persists while the drug is being taken and for variable period after administration of the drug ceases, depending on the dosage adopted Its action in this respect is superior to quinine or atebrin for gametocyte carriers will continue to infect mosquitoes while these drugs are being administered On the other hand as a true gametocide, it is inferior to plasmoquine

5) As a result of extensive field trials by Fairley (1946 1947) working with the Medical Research Unit of the [illegible]
for clinica [illegible]
suffices I [illegible]
days com [illegible]
infections owing to the long persisting exo-erythrocytic phase no short course of the [illegible]
[illegible] there would be too few falciparum gametocytes readily to infect mosquitoes after this 33 days period had elapsed

6) *Causal prophylaxis and suppression* Paludrine in dosage of 100 mgm weekly proved adequate for the full suppression of malaria in volunteers repeatedly exposed to heavy infection by mosquitoes with viable sporozoites of *P vivax* and *P falciparum* in their salivary glands Subinoculation arising from the extra erythrocytic forms is inhibited in both vivax and falciparum infections this being fundamentally different to the suppressive effects of atebrin

sanctochin resochin quinine and sulphadiazine With the latter group of drugs suppression or cure is achieved by schizonticidal action where as with paludrine there is a direct effect on the extra erythrocytic forms as well In falciparum malaria the extra erythrocytic forms are destroyed and radical cure results (complete causal prophylaxis) In vivax malaria with a regimen of 100 mgm weekly the delaterious inhibitory effect is temporary the extra erythrocytic forms surviving and later giving rise to erythrocytic parasites and overt malaia (partial causal prophylaxis)

7) The difference between the effective therapeutic dose and the toxic dose is very considerable Minor toxic effects have been noted to follow the administration of 300 mg daily for the therapy of overt malaria These consisted of vomiting and signs of irritation of the renal tract These toxic phenomena rapidly disappeared on reduction of dosage or subsidence of the overt attack of malaria A transient increase in myelocytes with maximal rise on the 7th 9th day was frequently observed In lower dosage regimens such as 0 3 gm daily for 14 days significant toxic symptoms were absent

Paludrine has been tried in India under the direction of malaria Institute of India According to Covell it is the only drug that can be used with entire safety to ensure complete causal prophylaxis against malignant tertian malaria having a definite lethal action on the pre erythrocytic forms In benign tertian infections it acts as a partial causal prophylactic only It will however effectively suppress all forms of malaria when given as a single dose once or at most twice weekly It is a powerful schizonticide in benign and malignant tertian malaria *and a single dose of the drug will control the clinical attack of both these infec*tions though there is as yet some doubt as to its efficacy in quartan malaria

Paludrine exerts no obvious primary effect on either the number or microscopical appearance of gametocytes in the patients' blood but mosquitoes feeding on individuals taking the drug are unable to transmit the infection

'Paludrine is remarkably free from toxic complications its range of activity measured as the ratio between the effective therapeutic and the toxic dose being far greater than with any other antimalarial drug yet known This property together with its action in controlling the clinical attack with a single dose and effecting complete causal prophylaxis in malignant tertian infections render it particularly suitable for widespread use under both rural and urban conditions throughout *India*

'As regards the prevention of relapse in benign tertian and quartan malaria paludrine possess little if any, advantage over other antimalarials Since however the occurrence of a relapse can be prevented by administering a small dose of this apparently harmless drug once a week there seems no reason why this should not be continued until the infection has completely died out

A number of other new anti malarial drugs have also been prepaired and tested

(2) Chloroquine (S N 7618)

Chloroquine was first synthesized in Germany some years ago but was considered too toxic for general use and was slightly modified under the name *of Sontochin During the recent war supplies of the latter drug were captured* in North Africa by the Allies and were subjected to detailed investigation in U S A The Americans found Sontochin effective in human malaria but did not agree with the original German verdict on Chloroquine and thought the latter superior and worthy of further development

"Chloroquine is a member of the 4-aminoquinoline series and has the

crine It appears to act in the same way as mepacrine but to be more effective and is said to be less apt to cause disagreeable gastro intestinal symptoms It is an effective suppressive drug when administered in a single dose once weekly

The Medical Department of the United States Army has now adopted Chloroquine-diphosphate as a standardized improved malarial therapeutic and suppressive drug It is supplied in tablets of 0 5 gm each containing the equivalent of 0 3 gm of the base The standard dosage adopted is as follows For an initial attack or acute relapse one tablet of 0 5 gm is given initially followed 4 hours later by another 0 5 gm For the next three days one tablet of 0 5 gm is given each morning at 9 A M (total dose 2 5 gm in 4 days) It is recommended that this dosage should not be exceeded For suppressive chemo prophylaxis one tablet 0 5 gm is recommended weekly With this regimen the blood is cleared of parasites in less than 24 hours and the interval between relapses is stated to be considerably longer than with quinine or mepacrine therapy Toxic symptoms are stated to be few infrequent and mild and rarely necessitate discontinuance of therapy Anorexia mild nausea and vertigo were rarely encountered and the only common toxic manifestation was pruritis without rash in less than ten per cent of the cases

(3) Metachloridine (S N 11,437)

Metachloridine

The formula for this drug is 2 metanilamido 5-chloro pyrimidine which is somewhat similar to that of sulphadiazine It is very active against several species of avian malaria In human malaria it has been disappointing in the treatment of malignant tertian infections but is said to be active in quartan. As mentioned above there is some evidence to suggest that paludrine is less effective in quartan infections than in benign and malignant tertian, and should this be confirmed metachloridine may prove of value in the treatment of quartan malaria either alone or in combination with other antimalarial drugs Unpublished reports on limited series of cases indicate that it has a very low grade of toxicity but further evidence is required before a definite opinion can be given on this point]

(4) Pentaquine

Pentaquine or SN 13,276 is a quinoline derivative having the chemical formula 6-methoxy 8 (5 isopropylamino-amylamino)-quinoline and is used as the diphosphate salt The drug is rapidly absorbed from the gastro-intestinal tract of experimental animals and appears to closely resemble plasmoquin in its absorption excretion and tissue distribution In man also it is rapidly absorbed plasma levels are quickly attained and fall to zero within 24 hours of stopping the drug Pentaquin is only one third as toxic as plasmoquin in the rat half as toxic in dogs and half to quarter as toxic in monkeys The toxic reactions are similar to those produced by plasmoquin

Antimalarial activity

Pentaquin was found to be more active than either quinine or plasmoquin against *P gallinaceum* and *P lophurae* infections In experimental trials in man with P vivax infections the drug was found to be at least partially effective as a causal prophylactic when administered in toxic doses (120 to 180 mgm a day) to persons bitten by heavily infected mosquitoes on the second day of drug administration

As a curative pentaquine was found to terminate individual attacks but was only partially effective in preventing relapses when given alone in doses as high as 120 mgm a day When combined with 30 grs (2 gm) of quinine a day however doses of 60 mgm a day of the drug were found to achieve complete eradication of the disease *in 16 out of 17* patients so treated

Pentaquine is too toxic a drug to justify its use for either prophylactic purposes or for prolonged suppressive therapy For cure of *P vivax* infections however a daily dose of 60 mgm of the base combined with 30 grs quinine daily in divided doses every 4 hours for 14 days is sufficient to produce radical cure of severe vivax infections The daily dose of 60 mgm of the base (80 mgms of the diphosphate salt), should not be exceeded *and the drug should only be* given under close medical supervision Besides plasmoquinine and paludrine this is the only other drug which has been shown to have action on the exoerythrocytic cycle

(5) "Cam Aqi"

Cam aqi 4 (3 diethylamino ethyl 4 hydroxylanilino) 7 chloroquinoline dihydrochloride dihydrate is yellow crystalline powder introduced by the Parke Davis Research Laboratories and found by them to be several times as effective
Absorption from the gut was very
reached The acute toxicity in
mepacrine and the chronic toxicity
even less

Simmeons and Chhatra (1947) tested the drug in human malaria in dosages of 10 mgm per kilo body weight In their very small series of cases they found that the blood was cleared of malarial parasites in 24 to 48 hours Further reports will enable the value of the drug to be assessed

13 Summary of treatment of Clinical Malaria

General management —The patient should be put to bed when the paroxysm starts preferably in a dark well ventilated room Bedding and clothing should be such as to give the least discomfort when the patient is drenched with sweat If possible the clothing should be changed frequently

The diet should be light with plenty of carbohydrate glucose may be given During febrile period only fluid should be given and plenty of water to drink in form of lemonade When fever subsides full diet should be given The bowels *should be kept working daily with calomel and salts in all cases* a preliminary purgative should be given *Aspirin may be given to relieve headache* Proper nursing is important and should be started immediately without waiting for result of blood examination

Quinine —Ten grains twice daily (20 grains in 24 hours) are quite sufficient in an adult Indian patient but in Europeans ten grains three times a day (30 grains in 24 hours) may have to be given daily In children and women smaller doses are required The drug should be combined with alkalis and continued for 7 to 10 days Quinine mixture—Quinine sulphate or totaquina 10 grains citric acid 30 grains magnesium sulphate 60 grains distilled water one ounce Alkaline *mixture*—soda bicarb 60 grains sodium citrate 40 grains calcium carbonate 3 grains and distilled water one ounce The alkaline mixture is given half an hour before the quinine mixture

In malignant forms quinine should be given immediately by the intravenous route in doses of 7½ to 10 grains; 1 to 3 injections may have to be given to produce disappearance of parasites from the peripheral blood After this the quinine should be given by the mouth and if this is not possible, by the intramuscular route till oral administration can be given. The treatment should be continued for 10 days For intramuscular use quinine may be combined with urethane to decrease the pain due to the acidity of the solution—Quinine hydrochloride 10 grains, urethane 5 grains and sterile distilled water 2 ccm

Atebrin—This drug should be given in doses of 0 1 gm (1½ grains) three times a day for 5 days (according to some for 7 to 10 days) in an adult If crescents are present the course should be followed by 0 01 gm of plasmochin twice daily for 3 to 4 days In malignant cases 0 1 to 0.3 gm of atebrin in soluble form should be given intravenously or intramuscularly followed by oral administration If relapses occur the whole course laid down above should be repeated with each relapse

Paludrine—Give 100 mgm of paludrine thrice daily for 10 days in case of M T infection, this will produce a radical cure In case of B T infection similar doses have to be given but 100 mgm once a week may have to be given for some time afterwards to produce a radical cure.

The follow ng [illegible] the sched le of dosage [illegible]
for [illegible]
(3 t [illegible]
mgn [illegible]
afte [illegible]
twic [illegible]
as for adults is recommended

Chloroquine diphosphate—For an initial attack or acute relapse, on the first day two doses of 0 5 gm are given with a 4—hours interval On the next three days a single dose of 0 5 [illegible]
4 days) Th [illegible]
used by the U [illegible]
of parasites [illegible] hours

14. Prophylaxis of Malaria

(1) General Measures

Elimination of mosquitoes

Anti Mosquito Measures—It is more economical to concentrate on the elimination of the main human malaria carriers rather than to campaign against all mosquitoes Such small doses of plasmoquine as 0 01 gm twice daily for a few days sterilize the sexual forms of *P. falciparum* so that they can no longer infect mosquitoes Sexual forms of other plasmodia are damaged by quinine and atebrin.

Some species of mosquitoes enter houses and prefer to feed on domestic animals (keeping of cattle near houses may afford protection to man) The breeding of dangerous species is checked by measures based on the study of habits of each species. In some species, such as *A minimus*, shading of streams prevents breeding Rice fields where the water is kept in continuous motion, are particularly dangerous and in Java the drying-off of the fields throughout a

As a curative, pentaquine was found to terminate individual attacks but was only partially effective in preventing relapses when given alone in doses as high as 120 mgm a day When combined with 30 grs (2 gm) of quinine a day, however, doses of 60 mgm a day of the drug were found to achieve complete eradication of the disease in 16 out of 17 patients so treated

Pentaquine is too toxic a drug to justify its use for either prophylactic purposes or for prolonged suppressive therapy For cure of *P vivax* infections, however a daily dose of 60 mgm of the base combined with 30 grs quinine daily in divided doses every 4 hours for 14 days, is sufficient to produce radical cure of severe vivax infections The daily dose of 60 mgm of the base (80 mgms of the diphosphate salt), should not be exceeded and the drug should only be given under close medical supervision Besides plasmoquinine and paludrine this is the only other drug which has been shown to have action on the exoerythrocytic cycle

(5) "Cam-Aqi"

'Cam aqi,' 4 (3 diethylamino ethyl 4 hydroxylanilino) 7 chloroquinoline *dihydrochloride dihydrate, is yellow crystalline powder introduced by the Parke* Davis Research Laboratories, and found by them to be "several times as effective as quinine and quinacrine in avian malaria" Absorption from the gut was very rapid and high plasma levels were rapidly reached The acute toxicity in laboratory-animals was about half that of mepacrine, and the chronic toxicity even less

Simmeons *and* Chhatra (1947) *tested the drug in human* malaria in dosages of 10 mgm per kilo body weight In their very small series of cases they found that the blood was cleared of malarial parasites in 24 to 48 hours Further reports will enable the value of the drug to be assessed

18. Summary of treatment of Clinical Malaria

General management —The patient should be put to bed when the paroxysm starts, preferably in a dark well ventilated room Bedding and clothing should be such as to give the least discomfort when the patient is drenched with sweat If possible the clothing should be changed frequently

The diet should be light with plenty of carbohydrate, glucose may be given During febrile period only fluid should be given and plenty of water to drink in form of lemonade When fever subsides full diet should be given The bowels should be kept working daily with calomel and salts, in all cases a preliminary purgative should be given *Aspirin may be given to relieve headache* Proper nursing is important, and *should be started immediately without waiting for* result of blood examination

Quinine —Ten grains twice daily (20 grains in 24 hours) are quite sufficient in an adult Indian patient, but in Europeans ten grains three times a day (30 [illegible] In children and women smaller [illegible] ibined with alkalis and continued [illegible] sulphate or totaquina 10 grains citric acid 30 grains [illegible] *grains distilled* water one ounce. Alkaline mixture—soda bicarb 60 grains, sodium citrate 40 grains, calcium carbonate 3 grains and distilled water one ounce The alkaline mixture is given half an hour before the quinine mixture

intravenous
route ... be given to
prod ... er this the
quin ... the intra
muscular route till oral administration can be given The treatment should be continued for 10 days For intramuscular use quinine may be combined with urethane to decrease the pain due to the acidity of the solution—Quinine hydro chloride 10 grains, urethane 5 grains and sterile distilled water 2 ccm

Atebrin—This drug should be given in doses of 0 1 gm (1½ grains) three times a day for 5 days (according to some for 7 to 10 days) in an adult. If crescents are present the course should be followed by 0 01 gm of plasmochin twice daily for 3 to 4 days In malignant cases 0 1 to 0 3 gm of atebrin in soluble form should be given intravenously or intramuscularly followed by oral administration If relapses occur the whole course laid down above should be repeated with each relapse

Paludrine.—Give 100 mgm of paludrine thrice daily for 10 days in case of M T infection this will produce a radical cure In case of B T infection similar doses have to be given but 100 mgm once a week may have to be given for some time afterwards to produce a radical cure

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as for adults is recommended

Chloroquine diphosphate—For an initial attack or acute relapse on the first day two doses of 0 5 gm are given with a 4—hours interval On the next three days a single dose of 0 5 gm is given each morning (total dose 2 5 gm in 4 days) This dosage should not be exceeded This drug is being extensively used by the U S Army and with the above dosage the blood is generally cleared of parasites in less than 24 hours

14 Prophylaxis of Malaria

(1) General Measures

Elimination of mosquitoes

... nore economical to concentrate on the carriers rather than to campaign against ... lasmoquine as 0 01 gm twice daily for a *P falciparum* so that they can no longer ... ther plasmodia are damaged by quinine and atebrin

Some species of mosquitoes enter houses and prefer to feed on domestic animals (keeping of cattle near houses may afford protection to man) The breeding of dangerous species is checked by measures based on the study of habits of each species. In some species such as *A minimus* shading of streams prevents breeding Rice fields where the water is kept in continuous motion are particularly dangerous and in Java the drying-off of the fields throughout a

tract one day each week has been made obligatory This is effective without damaging the crop.

Bright and well ventilated houses, [illegible] of mosquitoes, rooms may be made m[illegible] of 18 mesh Swatting of resting r[illegible] insecticides are useful measures Recently the "Freon bomb", a small round drum containing pyrethrum concentrate dissolved in compressed freon gas, has been evolved by the American Army On opening the nozzle, the insecticide is projected 6 to 8 feet in the form of a fine fog or aerosol which kills all mosquitoes in 100 000 cubic feet D D T is another recent and very efficient insecticide

Larval control is carried out by getting rid of all collections of stagnant water in or near the houses which form the breeding ground A preliminary survey by an expert is essential if large scale operations of mosquitoe destruction are to be carried out, as even such measures as clearing of jungle or drainage may produce increase of the mosquitoe vectors Drainage of marshes and collections of water, filling of burrow pits training of streams *alternate flooding and flushing of streams* etc, protection of wells and cisterns, such biological measures as introduction of fishes which feed on mosquitoe larvae oiling and use of chemicals are some of the methods employed The operations should extend well beyond the area to be protected

A wide variety of oils are used *for destruction of mosquito larvae. Kerosine oil* is largely employed either alone or with the addition of 1 to 2 per cent cocoanut or castor oils to improve its spreading power Anti malarial oil (A M M) is a mixture of diesel oil solar oil and kerosine

Malariol a mixture of petroleum and *waste motor oil* has also been extensively used Oiling kills mosquito larvae by suffocation and by its toxic action The oil may be applied by spraying under pressure through an atomizing nozzle Oil swabs or cotton wool steeped in oil and weighted down by a stone when thrown into water are ideal for springs and running streams A "gudda made of sacking will soak up 2 gallons of oil and last 3 months, the oil gradually exuding and spreading as a fine film over the surface of the water

Paris green (copper aceto arsenite) is mixed with one hundred times its weight of finely sifted road dust soapstone or powdered charcoal and is sown by hand down wind over the water surface at the rate of 17 grains of Paris green per square foot of surface The particles are eaten by the anopheline larvae and act as a direct poison In the quantities used this preparation is harmless to other forms of aquatic life. In America special dusting machines and aeroplanes are largely used for this purpose and an aeroplane equipped with a special *automatic machine, can cover 20 square miles a day Greenglide* another arsenic copper mixture (arsenious oxide 55 37 per cent copper oxide 31 12 per cent water soluble arsenic 1 per cent) marketed by Graven and Co has an advantage over Paris green in that it will float for weeks *Copper sulphate* is especially useful for tanks where drinking water is stored or where sheets of algae are sheltering the larvae

Mosquito netting containing '25 to 26 holes to the square inch' should be employed to cover beds at night and edges of the net either tucked in or so weighted that they touch the floor During the day time the net should be rolled up so that no mosquitoes are entrapped

Pyrethrum powder is most effective for fumigation and may be used dry and puffed into the air of a room with a handspray or a nebulizer Many proprietary sprays, are on the market and most of them are *mixtures of kerosine oil and pyrethrum* The following may be mentioned Flytox Shell tox, Pyrotox, etc.

[illegible] which are smeared on the hands and face, [illegible] oil of citronella or pyrethrum [illegible] greasy [illegible] cent [illegible] cent, [illegible] spirit [illegible] soap of camphor [illegible] ective *affords some protection* when nothing else is available. [illegible] for at least 5 to 6 hours —Stearic acid 27 parts caustic

soda 0 77 part, gum tragacanth 48 part, pyrethrum extract one per cent 16 parts, oil of citronella 6 16 part, aqua 100 parts

The education of the public especially students in the schools by simple illustrative posters, magic lantern lectures, cinema films etc., is most important The people in endemic localities should be made malaria minded

Of the newer mosquito repellents recently introduced, *dimethyl phthalate* and *dibutyl phthalate* have been found best in practice, and when thinly applied to the skin, they have been found to give full protection for six hours or more. Both of these chemicals can also be used after incorporation into creams, but there is little advantage in this. They

solution in Arachis Oil.

D.D.T or Dichlor-diphenyl trichlorethane is widely used for the destruction of larvae and adult mosquitoes, and exerts its lethal effect probably through its action on the peripheral and muscular systems The action is slow, but persists for long periods After a single spraying in the concentration of 100 mgm per square foot, the mosquito popullation of treated hours is greatly reduced for two to three months as compared with one week with the use of Pyrethrine alone D D T may also be incorporated with the whitewashing or paint applied to the walls

In 1942, *Gammexane*, a gamma isomer of hexachlorocyclohexane was introduced as an

(2) Chemo-therapeutic Suppression and Prophylaxis of Malaria

Cinchona alkaloids

Quinine (cinchona febrifuge and totaquinine) are used in India and other malarial countries as a prophylactic, and though these have considerable value, the protection afforded cannot be considered absolute Under war conditions quinine prophylaxis has not proved satisfactory for troops operating in open warfare, and it should not be solely relied upon

Six grains of quinine hydrochloride or the sulphate, should be taken about 2 hours before bedtime daily, during the malarial season Koch's system advises 15 grs twice weekly on two consecutive days during the week These doses, are, however, now considered insufficient and 10 grs daily are advised on entering the hyperendemic area, and continued for one month after leaving Taken in this fashion the clinical symptoms of subtertian malaria are mitigated and the risk of blackwater fever is reduced

The following figures cited by Celli, indicate the relative value of prophylactic measures —Mosquito protection plus quinine prophylaxis, 1 76 per cent infected mosquito protection alone, 2.5 per cent infected, quinine prophylaxis alone 25 per cent infected no protection at all 33 per cent infected

Plasmoquine

Plasmoquine attacks the gametocyte stage (even in doses of 0 01 gm twice daily for 2 or 3 days') and it was hoped that it would prove an ideal prophylactic This drug also has no action on the extra-erythrocytic cycle and has no causal

prophylactic value Even for suppressive prophylaxis such large doses have to be given which produce toxic effects

Mepacrine hydrochloride given in doses of 0 3 gm daily over a period of 5 to 7 days before being bitten by infected mosquitoes, considerably prolongs the incubation period of an attack For complete effectiveness, the dosage has to be increased to a total of 6-8 gm over a period of 22 days before and 30 to 60 days after exposure.

For clinical or suppressive chemoprophylaxis 0 4 to 0 7 gm of atebrin weekly (0 1 gm daily) or 0 2 gm twice a week is said to be sufficient and does not interfere with general health For children, doses ranging from half a tablet (0 05 gm) weekly for infants aged 2 years, up to two tablets weekly for children of 8 years of age, are advised The effect of atebrin prophylaxis may be judged by the continued absence of clinical symptoms of malaria, the continued absence of malarial parasites in the peripheral blood, and the stability of the haemoglobin index, inspite of exposure to malarial infection To be effective the atebrin level in the blood *should be between 25 and 30 micrograms per litre of plasma*

The following conclusions were drawn from experimental investigations carried out in Australia during the War —

Quinine sulphate given in solution, 10 grains daily commencing two days before the first infective bite, failed to prevent overt attacks of *falciparum* malaria Similar doses completely suppressed *vivax* attacks in some cases but not in all

... ne, sulphamerazine and sulphamezathine) in doses ... malaria in 20 out of 21 volunteers and cured 17 of ... phylactics they destroy the asexual blood parasites.

... peri... also ... of t ... did not rob mepacrine of its e...

... in hyperendemic areas ... discipline

The following procedure of chemoprophylaxis was adopted in the Royal Navy —

Suppressive treatment with atebrin (mepacrine) is recommended for naval personnel who are exposed to malarial infection One tablet of 0 1 gm (1½ grains) should be taken daily at the evening meal This routine should be continued throughout the period of ... incidence

In some persons mepacrine causes nausea and vomiting or colic and diarrhœa, but this is an initial intolerance often due to taking the drug on an empty stomach or in too large a dose, temporary reduction of the dose leads to tolerance, and less than one per cent of persons are unable to continue taking it

The routine should be modified in certain circumstances· when clinical attacks occur they are treated and the suppressive doses are resumed afterwards, if the incidence of

clinical attacks is high, say after return from strenuous combat it may be reduced by increasing the daily suppressive dose to three tablets (0.2 gm) daily after meals for 3 5 days and then returning to 0 1 gm a day as before

Paludrine Hydrochloride has been found to be an effective causal prophylactic and chemo therapeut c suppressive as a result of extensive clinical trial The manufacturers recommend a dosage of 100 mgm (1 tablet) twice a week in hyperendemic areas and 100 mgm once a week in others For children below 10 years of age half the adult-dose is satisfactory With such suppressive doses even when continued for prolonged periods toxic symptoms are not encountered

Chloroquine diphosphate For suppressive chemo prophylaxes as a result of extensive cl nical and field trials the U S Army Med cal Department recommend chloroquine d phosphate in a dosage of 0 5 gm weekly

(3) Prevention and Control of Malaria in World War II

According to Saperol(1946) the experience and research during World War II have made important contributions in connexion with prophylaxis and control of Malaria There is more effective anopheline control by the advent of D D T There is more effective drug prophylaxis as a result of the development of new drugs and improved methods in the use of drugs which formerly produced only mediocre results It should however be remembered that effective malaria control is attained only to the extent to which organized methods are employed and carried out by a team of specialists

Role of DD

Prior to World War II, the main attack on anophelines was almost solely confined to measures which would destroy larval forms Measures against adult mosquitoes were difficult and infrequently attempted With the introduction of DDT, however the attack has become twofold *i e*, against both larvae and adults

[illegible] itage of DDT, has been found [illegible] applications For example [illegible] in diesel oil will now suffice [illegible] obtained by 20 to 40 gallons [illegible] s enable an important saving

Where there are large areas to cover airplanes have proved effective for the dispersal of DDT These wartime trials indicate that airplane in the postwar period will serve as an important aid to malaria control not only as a device for saving time and labour but also for the control of areas otherwise inaccessible

In the use of DDT [illegible] possibilities are being explo[illegible] mpregnating bed nets by sp[illegible] and parti cularly by spra[illegible] ult mosquito population coul[illegible] means that malaria transmission in an uncontrolled area can be stopped far more readily than has ever before been possible Current experiments in which complete control is being attempted solely by adult kill show that whenever larvicidal measures are impractical for reasons of cost or inaccessibility effective control by adult eradication can nevertheless be achieved

Th[illegible]

[illegible] and larvae in a single operation

A great deal of wartime research was directed toward the development of new repellents Unfortunately repellents at present appear to have so many limitations that their general usefulness for protection against malaria does not seem promising It is difficult to be certain that persons will use repellents

Present day repellents however are vastly superior to those used in the past and will be beneficial if used carefully

Wartime experience and research has greatly extended the usefulness of drugs for prophylactic purposes It is now possible for military forces to operate in highly malarious uncontrolled areas without significant malarial morbidity

It has been demonstrated that (*a*) both mepacrine hydrochloride and quinine are fully preventive against malaria due to P falciparum merely by prolonging the administration of the drug for approximately a month after the last exposure (*b*) in malaria due to P vivax these drugs are capable merely of suppressing clinical symptoms and that overt attacks are inevitable when administration of the drug ceases (*c*) mepacrine hydrochloride is superior to quinine as a suppressive and (*d*) the mechanism of protection is not due to a destruction of infective organisms but to the reduction of parasitaemia to a level insufficient for the production of clinical symptoms

It has further been shown that various factors such as combat fatigue or *any other type of hard physical exertion extreme cold blood loss* and other factors do not precipitate clinical break throughs in persons taking a drug as a suppressive measure Failures with quinacrine hydrochloride which is taken in the recommended suppressive dosage are extraordinarily rare Clinical break throughs are due to failure to take the drug in the vast majority of cases

This knowledge gained during World War II has important implications in the present day control of malaria in civil communities *e g* labour forces working in highly endemic areas Where malaria due to P falciparum is prevalent complete prot
the eventual problem of
must be faced when sup

Mepacrine hydrochloride has the serious drawback of staining the skin In addition many persons on initial administration of the drug experience gastro-intestinal symptoms For this reason plus its inability to render any more than temporary protection in malaria due to P
other drugs which would not have these
quine has the advantage that it will not
lead to gastrointestinal symptoms as doe
to be administered only in a single weekly
as careful supervision of weekly adminis
daily supervision required in the use of m
hydrochloride permits suppressive cure
affords only temporary protection against malaria due to P vivax

The two drugs however are not causal prophylactics Paludrine in P *falciparum* acts as a true causal *prophylactic Preliminary experiments against the*

infections due to P vivax indicate that it exerts at least a partial causal prophylactic effect and does so in doses which appear to be nontoxic

Entomologic Control

A team of expert workers is required for the control to be effective and economical The entomologist is able to locate the single species transmitting malaria and to concentrate efforts on the species In addition to the entomologist a malariologist directed the overall program and an engineer carried out control operations

The present day significance of these wartime achievements in the control of malaria is that they re emphasize the fact that a like approach in civilian communities is essential With such methods, according to Russell "one may reasonably hope that, with suitable organization, malaria will be eradicated from the United States within next decade, and that in many tropical areas, even though economically depressed this disease now of the greatest importance may become in the next half century one of the least of public health problems'

15 Special Forms of Malaria

Pernicious Malaria

The pernicious types are the gravest forms of malaria. In a patient with a single [illegible] Almost all cases of pernicious [illegible] in rare and exceptional cases [illegible]ious symptoms and death may [illegible]ghly malarious places and in the most malarious season of the year but they may occur in places where the disease is not so intense The pernicious symptoms come on sometimes with dramatic suddenness.

Symptoms prod[illegible] of [illegible] inte[illegible] ma[illegible] types of pernicious malaria —

Cerebral Malaria

I Pernicious malaria is called cerebral when symptoms of cerebral involvement are dominant It is due to aggregation of red cells infected with malarial parasites in the brain which lead to inflammatory and degenerative changes The peripheral blood may not show a heavy infection, the occurance of more mature forms especially the schizonts of *P falciparum* in the blood however is of grave significance and is an indication of threatening cerebral malaria The symptoms set in during the course of fever rarely in the beginning and there is a history of mild intermittent fever Such symptoms as nervous twitchings, light headedness and drowsiness usually precede the onset of graver symptoms of cerebral types The following are the sub-types of cerebral malaria —

Hyperpyrexial

(*a*) In hyperpyrexial type the temperature instead of stopping at 104° or 105° may continue to rise and passing 107° rapidly mounts to 110° or even 112° followed by violent headache maniacal or muttering delirium unconsciousness and coma, which develops rapidly The patient dies within a few hours of the onset of symptoms Such cases may be mistaken for sunstroke or heatstroke

Comatose

(*b*) In comatose type the temperature does not usually rise above 104° the patient, however is apathetic from the beginning and rapidly becomes comatose. The coma may pass off with crisis of sweating or an asthenic condition may set in and death from *collapse may occur The cerebrospinal fluid comes out under increased pressure and intra* cellular malarial pigment is a striking and diagnostic feature (Manson Bahr) The large mononuclear cells are increased and there is a definite increase in the albumin and globulin content.

Other cerebral forms

(*c*) In other cases delirium is the chief feature and there may be mild excitement or a severe degree of mental confusion The condition known as 'running amok' may be produced as a result of malaria. Convulsive seizures of an epileptic or tetanic type with or without delirium or coma are specially common in children and are too often misdiagnosed, with fatal consequences. Forms resembling cerebrospinal fever delusional insanity acute alcoholism and psychosis have been described In some cases there may be mental changes of a permanent character Syndromes of localised nervous involvement such as

of low tension A mild degree of albuminuria is not uncommon but true nephritis is rarely seen.

If chronic malaria is not treated and the disease allowed to develop unchecked, it passes on to malarial cachexia The patient is anaemic and the complexion is dusky œdema occurs round the ankles or may be more generalised The abdomen is prominent (enlargement of the liver and spleen) the patient emaciated and asthenic, there is diminution of haemoglob ... kilocytosis polychromatoph lia, punctate ... large mononuclears are present. The ... f urobilinogen and urobilin.

Other symptoms are visual disturbances due to intra ocular haemorrhages and malarial amblyopia. In children growth is inhibited. Adolescents show hypoplasia of genitals and retardation of onset of puberty *Adults may suffer from* impotence and lack of sexual desire and rarely atrophy of the testes. Women have a tendency to sterility or miscarriage.

Certain mental changes are seen in malarial cachexia, *e.g.*, sensation of fatigue dislike of mental effort and inability to concentrate unreliable memory and occasionally aphasia.

In malarial cachexia, symptoms resembling beri beri (cardiac weakness) may develop and gangrene of the extremities may set in severe cases Liability to rupture of the spleen as a result of relatively *mild injury is met with* (Spleen puncture is dangerous) Schizogony is observed in peripheral blood without the usual paroxysms

Masked malaria is usually manifested by such symptom as neuralgia of the trigeminal type, the attacks of which may occur regularly for sometime then disappear only to return later Other symptoms are vomiting migraine, attacks of tachycardia herpes zoster etc. The condition is amenable *to quinine though* parasites may not be found attacks of neuralgia due to other causes may respond to quinine

Nervous sequelae of malaria are caused by long continued attacks and are seen in India. The sequelae include mental symptoms aphasia, dysphasia and symptoms of *disseminated* sclerosis Mental conditions that are sequelae of malaria are depression (melancholia and apathy) but confusional types may also occur rarely states of elation or excitement are produced Caution has to be exercised before ascribing the symptoms to malaria and other concomitant malarial symptoms and signs of direct connection with previous attacks must be established

Numerous diseases, aetiology of which is still obscure or incompletely known have been ascribed (specially by ex service men seeking pensions) to be sequelae of malaria.

In ...

obviously not due to malaria

(2) Malaria in Children

There are a few instances reported by reliable workers where infection in the infant came undoubtedly from the mother Clark, studying the pathology of malaria infected placentas found that although the maternal side of the placenta may show abundant plasmodia the foetal side is entirely free in every case He and others have shown that placenta is an effective barrier to the transmission of malarial parasites from the maternal to the foetal circulation and only some injury to the placenta allows the parasites to reach the foetal blood This also has been shown to be the case with monkey malaria. In *P vivax* infection Das Gupta considers that placental barrier is injured more by chronic rather than acute infection

Children are extremely susceptible to malaria and in hyperendemic areas every child born in the area contracts malaria shortly after birth, and will go on contracting fresh infections

... dia have shown that practically 100 per cent ... the age of two years are infected with ... e children are continuously febrile what ... After the age of three years the infection ... ge parasite count is relatively low At the age of six to ten years the actual infection rate is still nearly 100 per cent, but the numerical

value of infections comes down to lower values These children usually have attacks of malaria about once a month. In the same area only about 50 per cent of the adults are found to be infected and show a very low average parasite count In adults, the attacks of clinical malaria are few and far between The children are thus more frequently attacked by clinical malaria than the adults in hyper-endemic areas Infant mortality from malarial infection is high in these areas, being almost double the figures in non malarious localities

Clinical aspec

The clinical features of malaria in children differ considerably from those in adults. The individual attacks are irregular, the duration of the attacks may be so short as to escape notice; there may be no chill and rigor and the stage of sweating may be absent. The fever may come on only at night so that the pyrexial attacks go unobserved. None the less the children progressively decline in health, and develop the features of chronic malaria and malarial cachexia, they are particularly liable to intercurrent infections which may be fatal The acute attacks may be very severe giving rise to marked cerebral, gastro-intestinal, hyperpyrexial, or comatose symptoms, with fatal results

Four types

C D Williams has recently given an excell[illegible] malaria in children (Lancet, March 9, 1940) [illegible] malaria can be distinguished (*a*) Acute malar[illegible] symptoms (*b*) Chronic malaria with parasites [illegible] be found but who improve under [illegible]

Symptomatology of malaria in children. Signs and symptoms may be absent or they may be so severe as to be fatal. Any of the following symptoms or any combination of them may be present.

Pyrexia

Fever of 100°-103°F is perhaps the most usual symptom rigors at the onset are not so common in infants as in adults The fever may subside in a few hours and the child may appear quite normal between the attacks Sweating during defervescence is also not [illegible]

Gastritis and Gastro-enteri

The gastro-intestinal tract of a child is more sensitive than that of an adult, and is much more liable to be upset by adversities psychic, traumatic or infective In an adult the attack of malaria may lead to little more than anorexia In a child it may produce serious interference with digestion and assimilation, besides causing vomiting, diarrhoea or constipation.

Encephalopat

Children are apt to have convulsions at the onset of an illness, and the malarial paroxysm is no exception Convulsions often replace the rigor at the onset of malaria in children These often take the form of clonic or tonic contractions, though they may be of an epileptic type.

Cerebral symptoms at the onset of malaria, however, do not necessarily mean cerebral malaria, but the two are difficult to distinguish and it is as well to regard malaria accompanied by convulsions as very serious, although many patients recover

Splenomegaly

[illegible]

Hepatomegal anaemia

[illegible]

Cachexia

Malarial cachexia is by no means uncommon in children especially in those older than 9 months. These children are lethargic, querulous, and apathetic, with a grey unhealthy look. The children become thoroughly run down and anaemic and there is considerable enlargement of the spleen and the liver, causing protuberence of the abdomen

Blackwater fever is almost unknown in infants rare in older children and relatively uncommon in adults born in a malarious area

Quinine atebrin paludrine and chloroquine are useful as prophylactic agents.

Dosage recommended to be taken daily at bed time.

	Age	Dose	Age	Dose
Quinine —				
	Birth to 9 months	gr i	2-6 years	gr iii
	9 months to 2 years	gr ii	6-14	gr iv

Atebrin —*0 025 to 0 05 daily or 0 1* gm *or twice weekly* according to age

Paludrine —50 to 300 mg daily according to age for curative therapy and 50 to 100 mg once a week for casual prophylaxis

[illegible] wed in the treatment of malaria in children differ [illegible] case of treatment of malaria in adults. Trea[illegible] of the parasites but where the child has to remain in malarious country after cure and thus is certain to be reinfected, therapeutic measures directed to cure of the symptoms of an attack are all that is practically useful Besides the complications and sequelae of acute attacks *viz* anaemia cachexia hepatitis etc. have to be treated

Quinine has been found to be quite satisfactory drug in treatment of malaria in children The only disadvantage are its unpleasant taste difficulties of absorption and some undesirable after effects Quinine ethylcarbonate (Euquinine is mostly inactive and is not advised) The fever itself might lead to diminished absorption of quinine Also helminthic infection or other gastrointestinal disorders would do the same so that oral medication may fail in its objective Hence parenteral medication has to be considered

Parenteral administration of quinine is the method of choice in severe cases in cases that do not react to quinine given by mouth and those in which the parasites persist inspite of treatment and in cases where gastro intestinal symptoms are such as to preclude the adequate absorption of quinine given orally Intra venous injection of quinine is usually very difficult to administer in children and is not free from risks The intramuscular route has to be preferred

Quinine by mouth The following prescription is advisable —Quinine sulphate 2 grains ferrous sulphate 1 grain acid sulphuric dilute 4 minims and water up to one dram For a baby of one month old the dose is one dram thrice daily for older children correspondingly increased doses are given This dosage will relieve fever and cause disappearance of parasites in a week Severe cases and the cases where quinine is not being absorbed should be treated by quinine parenterally

Children tolerate atebrin well Dose 1 to 4 years 0 05 to 0 1 gm 5 to 10 years *0 2 gm and over ten years,* 0 3 gm daily It can also be given intra muscularly in doses of 1 ccm up to two years of age 2 to 4 ccm upto 12 years of a *0 3 gm in 9 ccm solution*

Paludrine The lack of bitter taste and its extremely low toxicity make paludrine a very useful drug for use in children It may be given in doses of 50 mgm for children below 2 years of age 100 mgm daily for children below 10 years of age and 300 mgm daily for children over 10 years

Treatment of complications Convulsions should be treated with sedatives by chloroform inhalations if necessary, and lumbar puncture A hot bath with ice cap to the head is often useful Anaemia is treated with ferrous iron and adjuvants In cases with severe anaemia transfusion of blood is indicated The transfusion is made through the vein in the anterior fontanelle if necessary

Blackwater fever is treated as in adults Malaria in children is as amenable to atebrin therapy as in adults The details of dosage have been given under Atebrin

16. Black-Water Fever

(1) General

Haemoglobinuria which occurs as a symptom of malaria is called black water fever It is precipitated by quinine and other drugs, but is essentially a severe manifestation of malaria or one of its outstanding sequelae The distribution of the disease runs parallel with that of severe malignant tertian malaria

Although the [illegible]

[illegible] Rhodesia Mauritius Madagascar the Southern United States the West Indies and South America The disease is very rare in mountains, [illegible]

The exact mechanism involved in the hæmolytic process is still obscure but the likely explanation is that in certain circumstances the red cells become sensitized to hæmolytic substances produced by the malarial parasites directly or by their action on the red blood cells. The rapid hæmolysis appears to be a phenomenon of a type similar to allergic or anaphylactic shock.

Pathology [illegible] globi[illegible] nor[illegible] hæm[illegible] the [illegible] proc[illegible] degenerated cells and debris so that anuria is produced In less severe cases the urine contains large amounts of albumin granular debris and tubular casts In the presence of acid urine acid hæmatin is deposited in the tubules producing renal insufficiency and azotaemia The red cells may be diminished by 2 or 3 million per cmm within 24 hours

The [illegible]

Post mortem findings are those of severe hæmolysis and malaria.

Symptomatology—The onset is sudden with rigor and rapid rise of temperature. The fever is generally of a *remittent type and may* last from a few hours up to 6 days or more. Three cardinal symptoms are hæmoglobinuria, fever and jaundice

In the mildest type there is slight fever and slight haemoglobinuria lasting a few hours and the attack *may* [illegible] ordinary malaria. In less milder types the fever an [illegible] two days and the general condition of the patient [illegible] ely severe types the fever lasts 3 or 4 days with pro [illegible] In the severest type, and nearly all fatal cases are [illegible] vere from the onset, and suppression *of urine* [illegible] collapse and hyperpyrexia are prominent features Occasionally some attacks are relatively mild at first but repeated paroxysms result in rapid deterioration of the patient s condition.

Vomiting is usual and there may be epigastric pain or severe lumbar pain Jaundice may be moderate or intense and appears early and lasts a few days after the fall of temperature

The urine is pink or bright red at first but soon becomes dark red brown or black. It is loaded with albumin and debris and tubular casts are numerous.

The pulse is of low tension weak and rapid There is a feel ng of prostration with anxiety and restlessness but the mental condition is usually clear Heart failure due to toxaemia and severe anæmia is a frequent cause of death

The majority of cases occur in areas where the disease is well known and diagnosis presents no difficulties The disease must be distinguished from hæmaturia in which case microscopic examination of the urine will show numbers of red cells In malaria with bile stained urine a piece of blotting paper dipped in the urine is stained yellow or greenish yellow whereas in haemoglobinuria it is stained red. Paroxysmal hæmoglobinuria and quinine haemoglobinuria are rare cond tions In yellow fever and leptospiral infections, the condition is one of haematuria and not hæmoglobinuria.

Prognosis is always grave but it depends on the severity of the attack, the age and general condition of the patient The average mortality ranges from 25 to 50 per cent in various local ties Hyperpyrexia, deep jaundice severe anaemia h ccough, and pers stently recurr ng paroxysms are unfavourable features as also is rapidly rising curve of blood urea.

(2) Treatment

The general management of a case of blackwater fever is the most important aspect of the treatment Absolute rest in bed avoidance of chilling and good nursing are essential. The patient should be kept warm and should not be moved after the disease has set in, the mortality rate is increased by transporta tion of patient He should not be allowed to sit up in bed, the writer has seen fatalities occuring just by the exertion of sitting up in bed The patient should not be allowed to get up untill temperature has remained normal for several days

Administration of fluid by mouth per rectum or even intravenously is an essential part of treatment Water containing 30 grains of sodium bicarbonate to the patient should be given frequently and the urine should be kept alkaline in reaction. Albumin water or barley water are retained better when given by mouth, also glucose Small quantities should be taken at a time In serious cases saline or glucose saline may be administered per rectum or intravenously As haemoglobinuria may recur on full diet it is advisable to carry on with milk, broths and fruit juices well into the convalescence.

The daily fluid intake should be 2000 to 6000 ccm per day and the actual intake should be so adjusted that 1500 to 2000 ccm of urine is passed The bladder should be emptied every four hours with a catheter if necessary, and its reaction should be tested If during the pre blackwater stage general and alkali treatment is instituted mortality is considerably reduced A mild saline cathartic should be given at once The consensus of opinion is that the action of atebrin

Quinine

in influencing the onset of blackwater fever is the same as quinine As a large number of parasites have probably been destroyed by general haemolysis antimalarial drug may not be necessary in the first day or two of disease If haemoglobinuria occurs in the course of a malaria paroxysm and parasite are present in the blood quinine or atebrin may be given If parasite are not found in the blood these drugs should not be given If quinine has already been given before haemoglobinuria and there are no parasites quinine should be stopped, if however parasites present it should be continued In patients who have an attack of blackwater fever quinine should be given with caution and in exploratory doses Every black water patient has a critical threshold dose of quinine

Atebrin and plasmoquin

Many authorities believe that fear of giving quinine in blackwater fever is exaggerated Quinine should, however be given cautiously so as not to produce nausea and vomiting Maegraith (1946) considers that there is no evidence that mepacrine is haemolytic and recommends its use in full doses Blackwater fever has, however, been reported in malaria treated with mepacrine alone and it may be better to use paludrine when malarial parasites persist during such an attack

Plasmoquine is definitely contraindicated and so is its combination with atebrin If plasmodia occur during convalescence etc atebrin may be given 0 1 gm on first day, two doses of 0 1 gm on the second day and three on the third fourth and fifth days This is the drug of choice in blackwater fever

Alkalis

[illegible]

sodium bicarbonate in adequate doses should be administered to keep the urine alkaline and in severe cases alkalis may have to be given intravenously An alkaline solution containing sodium chloride 5 75 gm sodium bicarbonate 18 25 [illegible]

A [illegible] per cent solution of glucose in warm saline has been [illegible] at a time Larger [illegible] these may prod[illegible] [illegible] urinary suppression

Whole blood transfusion

Transfusions of whole blood may be given when there is rapidly developing severe anaemia Washed packed red blood corpuscles suspended in normal saline have been recommended. Blood transfusion is especially useful in toxic and relapsing type of cases but it is contraindicated in toxic and anuric blackwater fever Care should be taken in grouping the bloods as auto-agglutination may occur in haemolytic conditions The blood may be given as citrated whole blood (500 ccm) every 24 hours or even twice a day in serious cases The patient should be carefully watched while the transfusion is being given, if any marked reaction occurs O 5 ccm of adrenaline may be given intramuscularly

Plasma Thro

When [illegible]

Vomiting may be alleviated by application of turpentine stupes and mustard plaster to the epigastric regions Morphia in very small doses may have to be administered to allay restlessness Antipyretics are contraindicated because of their depressing effect on the heart

Specific drugs used are cholesterin and cortin, 15 grain doses of cholesterin administered in thick suspension or in milk four hourly act as anti haemolytic. Cortin is believed to counteract degenerative changes in the adrenal cortex. Cholestrin may also be given intramuscularly in warm olive oil (5 per cent solution)

The convalescence should be prolonged and gradual, and return to normal diet and life very slow, because otherwise there is great tendency to relapse. Patients who have previously had an attack of blackwater fever should not be allowed to return to a country where malaria is prevalent Such patients should also not be transported suddenly from a hot to a cold climate

Prophylaxis—All cases of malaria, especially *P falciparum* infections should receive adequate drug treatment If malarial prophylaxis is properly carried out, blackwater fever does not occur This has been amply shown ... attack ... atebrin or paludrine ... nolic

Pre blackwater state should be recognized This consists of toxaemia slight jaundice, enlarged and tender liver and dark urine If this occurs antimalarial therapy with complete rest and alkali treatment, should be instituted

17. *Induced Malaria*

(1) General

Von Jauregg (1877) first drew attention to the favourable effect of malaria on certain mental disorders but systematic clinical trials were not began till 1917 For artificial induction of malaria in man two methods have been employed—

(1) Inoculation of blood containing malarial parasites either subcutaneously or intravenously The amount of blood required for this purpose varies from 0.5 to 5.0 ccm For ... 0.5 to 3.0 ccm of blood suffices but for subcutaneous inoculation 3 ...

virulent than it it is taken out ... malaria induced in this way averages between 4 to 10 days in case of intravenous injec... but it may take as long as 50 days in case of subcutaneous injection

(2) By means of infested mosquitoes the sporozoites being introduced by the bite of ... mosquito may be injected. In England ... will not develop in this mosquito at low ... for inducing malaria. In endemic areas ... culty in inducing of malaria on account ... patients In such cases blood containing ...ry carefully watched and frequent blood ... were encountered The danger of mixed

second inocculation or in immune people

In the treatment of cases of dementia paralytica, usually 8 to 12 attacks are allowed and in case of quotidian as many as twenty the writers experience in India is that it is generally not advisable to give more than six to eight paroxysms Spontaneous cures

Application to neurosyphilis diseases

Rarely first inoculat on may fail and a second or even a third may have to be given and if that fails infection through mosquitoes may have to be tried.

The symptoms produced are generally mild but the induced B T fever should not be considered harmless The attacks should be cut short atonce if severe anaemia and jaundice appear and the number of parasites in the blood is large. Rarely rupture of spleen has occured.

Symptoms and course

(2) Treatment

Infection produced by direct inocculation of blood is easy to cure permanently as there are no relapses Such small doses as 3 to 10 grains of quinine often stops the fever permanently in case of Indian strains, the relapse rate being only 2 to 4 per cent In other cases 0 6 to 1 0 gm of quinine or a few days course of atebrin will cut short the fever permanently Some strains e g Madagascar strain react less to quinine and better to atebrin and neosal varsan (Nocht & Mayer) Occurence of blackwater fever has been observed in induced malaria especially after quinine, but in the writers experience in Calcutta it never occured

Fever and high temperature probably act by their deleterious effects on the spirochaetes responsible for the disease and similar effects have been observed with non specific protein therapy (bacterial vaccines) and pyrogenic drugs Brutsch and Bahr have demonstrated proliferative changes in the capillary endothelium in the brain substance after induced attacks These must be regarded as local reaction of the reticulo endothelial system, perivascular infiltration occurs After these changes resolve, partial regeneration of ganglion and neuroglia cells may occur

Effects on general Paralysis

When such treatment is being carried in the paralytics, they must be protected with wiregauze mosquito netting to prevent mosquitoes being infected and transmitting infection to healthy individuals

18 Antimalarial Drugs in Simian Malaria

A few words may be said about the action of these drugs on ape malaria. It has been shown that *P knowlesi* produces a very intense and virulent infection in *Silenus rhesus* causing death of the animal if untreated. This plasmodium appears to be more closely

related to that occurring in man than plasmodia occuring in birds, which are usually used for testing antimalarial drugs. The results obtained should therefore be more readily applicable to man. Chopra and Das Gupta (1933) showed that the destructive action of atebrin on *P. knowlesi* was exceptionally powerful. Usually two doses of 0·025 gm of the drug given intramuscularly or intravenously are sufficient to control a very heavy infection which may amount to a million parasites per cmm of blood. The drug affected equally the schizogony and
more prolonged
whereas quinin-
treatment with
and multiplied
if prompt trea
easily one dos-
g ... the virulence. *In contra*
d
h
i
i
r
i
a
c
a
i
r
invariably falls to a negligible number

Stimulated by the results of these experiments, further work has been carried out on the concentration attained by these drugs in the circulating blood at *different intervals* of time in relation to parasite count. With regard to quinine, Chopra, Ganguli and Roy (1935) have shown that there is no direct relationship between the concentration of quinine in the blood and the parasite count at any particular time. The highest concentration of the alkaloid attainable without producing toxic effects produced no apparent reduction in the number of parasites nor degenerative changes in them. The action of quinine thus appears to be synergistic to other defensive mechanisms set up in the body. In therapeutic doses quinine augments these processes or possibly it acts on the parasites in such a way as to render them more vulnerable or unable to propagate. Studies on the concentration of atebrin *in the blood by Chopra, Ganguli and Roy (1936) show that the highest concentration of* atebrin occurs between half an hour and six hours after the injection of atebrin. The *number of parasites per cmm of blood distinctly* ... *in the majority of cases in the* first 6 hours when the concentration of atebrin i
the parasites are reduced to a negligible number
falling off. It is therefore reasonable to state
some direct lethal action on *Plasmodium knowlesi* in vivo. This has been further confirmed by Chopra, Das Gupta and Roy (1936) who showed that atebrin solution in a dilution of 1 in 50,000 *in vitro* is capable of destroying the parasites even when the infection is heavy. The smears of blood which were kept in contact with atebrin showed degenerative changes in the parasites. This work is being further elaborated.

Three important points which come out of this work are

(1) Atebrin has a more powerful and more rapid effect on *P. knowlesi*.
Whereas *quinine takes 24* hours to produce its effect, atebrin is effective in 6 hours and concentration of this drug runs parallel with the decrease in the number of parasites.

(2) Atebrin has some direct action on *P. knowlesi (1 in 50 000 concentration)*; quinine has not. In fact the first effect of quinine administration may be an actual stimulation of growth of parasites.

(3) A fatal relapse is more common after atebrin than after quinine. *The action of quinine*, though less powerful and less rapid, appears to be more prolonged and lasting. Whether all these are applicaple to human malaria remains to be seen.

19. Present Position of Antimalarial Drug Therapy

The present position of antimalarial drug therapy may now be summarised

The following groups of drugs are used in the treatment of malaria —

(1) Cinchona alkaloids

(2) Synthetic antimalarials

(i) Plasmochin and allied compounds—The amino-quinoline derivatives

(ii) Atebrine and similar compounds—Acridine derivatives

(iii) Sulphonamides

(iv) Paludrine

(3) Cinchona Alkaloids Versus Synthetic Antimalarial Drugs

(1) Cinchona Alkaloids

The importance of the fact that all alkaloids have marked antimalarial properties is very great to India where the economic condition of the pepole is low and purified quinine preparations, on account of their high price are beyond the means of ordinary people. The reasons why quinine is more expensive than the total alkaloids of the bark are —(i) that its proportion in the bark usually is a little more than half of the total alkaloids *Cinchona succirubra* and *Cinchona officinalis* barks for example, contain about 5 to 6 per cent of total alkaloids of which only 3 per cent is quinine *Cinchona ledgeriana* contains somewhat higher proportions (ii) The cost of its separation from other alkaloids and purification further add to its price It would follow therefore that if the total alkaloids are used they will be cheaper than if only quinine is used by itself It was for this reason that 'cinchona febrifuge' was used in India and the League of Nations have introduced *totaquinina* which contains 70 per cent of the total alkaloids of which 15 per cent must be quinine By this means it is hoped that the treatment could be made less expensive and extended among the masses

Some of the other alkaloids of the cinchona bark which occur in smaller quantities than the four alkaloids stated above, for example cupreine sulphate in doses of 1 gm was found to be effective in human malaria but it is much more expensive and toxic The same is the case with other such alkaloids

The disadvantages of the cinchona alkaloids are —

Disadvantages

(1) They have no action on the sporozoites injected by the mosquitoes and therefore they cannot have true prophylactic action in this disease This was demonstrated by Yorke and Macfie (1924) who showed that 18 grains of quinine daily for 5 days before and 7 days after the mosquito bite failed to avert an attack of a malaria, but if the drug was continued for 10 days, the disease did not develop This shows that these alkaloids have little effect on the injected sporozoites but act on the asexual forms liberated from the infected red blood corpuscles

(2) Cinchona alkaloids have little effect on the sexual forms of malignant tertian parasites They however, impede the formation of the pre gametocytes

(3) They do not prevent relapses

(4) These alkaloids do not act uniformly on all strains of malaria

After the World War I there
loids especially quinine and it was
certain forms of malaria Furth
was not due to any fault of the drug but due to its improper use.

be tried in those cases where administration by the mouth is not desirable or possible as it is liable to produce serious mutilation of parts Intravenous method should only be used for severe and urgent cases Parenteral method should not be used for routine administration of these drugs Intravenous injections must only be employed where the patient is comatose, or very gravely ill when an immediate response is necessary Any evidence of impending cerebral malaria is an imperative indication for injection treatment

On the appearance of acute symptoms of primary infection quinine has a definite action from the third day onwards (second paroxysm of fever) in benign tertian malaria Its action is less rapid according to the strains of malignant tertian concerned *and symptoms may continue until the fifth dose (third or fourth* paroxysm)

As regards the time of administration of these alkaloids by the oral route it is advisable to give them 2½ to 3 hours after a meal when the gastric contents are acid the digestion has been complete and the stomach is nearly empty If given at this time they rapidly mix with the contents of the stomach and pass into the small intestine from where they are quickly absorbed into the circulation There is less liability of their irritating the stomach if administered in this way

Dosage—Experience shows that in the case of Indian strains of malaria a 7 to 10 days course of treatment with 20 grains of the alkaloids daily is effective Larger doses are not only wasted but may do harm According to the Fourth *General Report of the League of Nations 0 5 gm of quinine hydrochloride some*time causes a temporary disappearance of trophozoites of benign and quartan infection but a mean daily dosage of 1 gm for 5 to 7 days is often necessary to *cause the trophozoites to disappear and not to make their reappearance* in the peripheral blood after a latent period of varying lengths in the course of first relapse In malignant tertian malaria 1 3 gm produces analogous results It is also agreed that definite advantage is obtained by combining them with alkalies

Preparations containing Cinchona derivatives During recent years a number of cinchona derivatives have been used in the form of proprietary remedies whose composition is secret Various claims have been made for these amongst others that they have destructive action on both the sexual and asexual forms of all parasites that they prevent relapses and that they have prophylactic value A number of preparations *are on the market and the writer has tested some* of these Our observations show that their action is practically the same as cinchona alkaloids they have no action on the gametocytes of malignant tertian they do *not prevent relapses* Being proprietary remedies they are very much more expensive Some of these preparations in the market are —*Malarcan* probably a derivative of quinine or quinidine *Tebetren* (quinine combined with acridine) *Paludex* (complex organo metallic preparation containing copper and oxyquino-

line), *Plasmodex* (a similar compound), and *Esanofeles* is a proprietary preparation containing 0 1 gm of quinine bisulphate, 0 001 gm of arsenious acid, 0 3 gm of iron citrate and some bitter principles It is used in India by medical practitioners in chronic malaria

(2) Synthetic Antimalarial Drugs

Groups according to activity.

These compounds may be divided into three groups —(1) Those which have action like the cinchona alkaloids on the asexual cycle, *e g*, atebrin and atebrin like substances, sulphonamide derivatives, etc. and (2) those whose main action is on the sexual cycle particularly of the malignant tertian variety, *e g* plasmochin (3) Those which act on the extra erythrocytic phase *e g*, paludrine pentaquin, etc

None of these compounds act on the sporozoites injected by the mosquitoes and therefore have no true causal prophylactic value except perhaps paludrine in a limited degree because of its action on exo-erythrocytic cycle

Their dosage as compared with the cinchona alkaloids is much smaller, but they are usually more toxic.

(i) The amino-quinoline derivatives

Effectiveness

(*a*) *Plasmochin* (*Pamaquin*) —The shortage of quinine supply during the war led to experiments in Germany for finding a synthetic drug which could be used in its place. [illegible]

Toxicity

On account of this peculiar property of damaging the gametocytes it renders them non infectious to [illegible]
in this respect [illegible]
the greatest virtu- [illegible]
form of ma'igna [illegible]
toxic effects and [illegible]
with quin ne anc [illegible]
more effective than quinine and the number of relapses is decreased Prolonged administration of this combination in therapeutic doses is likely to produce toxic effects but these are not so marked as a combination of plasmochin with atebrin. Plasmoquin by itself thus holds a minor place in the symptomatic treatment of malaria Cilional and Certuna are similar drugs, but are not so effective

Quinine & plasmochin It has been found in India that a combined course of quinine and plasmochin (pamaquin) was more effective in preventing relapses in benign tertian malaria than quinine alone Ten grains (0 65) of quinine and 10 mgm of plasmochin three times a day for ten days were recommended Later investigations confirmed these conclusions and found that during the six months following a combined course only 10 per cent of cases relapsed as compared with 30 per cent treated with mepacrine alone The combination of quinine and plasmochin is, however, more toxic than either of plasmochin and mepacrine

(b) *Chloroquin*—(SN 7618) 7-chloro-4-(4-dimethylamino 1 methylbutyl amino) quinoline This compound was used by the German forces in North Africa as an antimalarial drug during World War II It had been prepared by the I G *Farbenindustrie and was known as Sontoquin Its composition was worked* out and its derivatives were prepared in the United States One of these—chloroquin—on clinical trials was found to be better than mepacrine—as curative

The following doses are recommended for the treatment of all forms of malaria Curative 0 6 gm of chloroquine base (1 0 gm. of chloroquine diphosphate) on the first day followed by 0 3 gm of base in 6 *hours for the next* two days 0 3 gm daily The total amount given is 1 5 gm. of the base or 2 5 gm of diphosphate salt in 4 days The parasites disappear from blood within 24 hours For suppression purposes 0.3 gm. (or 0 5 gm of the salts) once a week is used for adults and for children under 8 years 0 15 gm of base (or 0 25 gm of the salt) The drug is usually given in tablet form

Toxic symptoms consist of mild headache blurring of vision dizziness diarrhoea pruritis urticaria etc The toxic symptoms are controlled by giving ammonium chloride to make urine acid.

(c) *Pentaquin*—(SN 13 276) 6-*methoxy* 8 (5 *isopropylaminoamylamino*) quinoline Both paludrine and chloroquin do not cure benign tertian malaria and the problem of finding a drug which destroys all forms of parasites in the body still remained Sinton showed that when quinine and plasmoquin (pamaquin) were given together in benign tertian malaria the relapse rate was *lower than with quinine or mepacrine alone Compounds allied to plasmoquin* were then studied in the United States and pentaquine was produced In both these compounds the ring structure is methoxy quinoline The same side chain is present in mepacrine plasmoquine and chloroquine.

The advantage of pentaquin is that it is much less toxic than plasmochin in bird malaria but a daily dose 0 06 gm of pentaquin is more toxic than 0 03 of pamaquin It is the most active compound yet discovered against bird malaria In volunteers infected with virulent type of *P vivax*, who were treated with full doses of quinine and pentaquin the infection was completely eradicated

Dosage 0 01 *gm of pentaquin* base (0 013 *gm* of mono phosphate salt) is given with 0 6 gm quinine sulphate three times a day for 14 days making a

(d) *Camoquin*—CAM AQI now called Camoquin (P.D) is a light yellow crystalline powder soluble in water It is a quinoline derivative the chemical formula being 4 (3′ diethalminomethyl-4′ hydroxyanilino) 7-chloroquinoline *dihydrochloride* dihydrate. The absorption distribution and excretion of the drug is similar to that of quinacrine but it causes little or no staining of the tissues Each tablet contains 0 05 gm of the base Chaudhuri and Chakraverty (1948) treated 54 malaria cases using 2 dosage schedules the first being 0 1 gm twice daily for 3 days and the second a single dose of 0 5 gm (about 10 *mg* per kilo body weight) The therapeutic response was very quick in all

Efficacy of atebrine

series The temperature came down to normal by the second day of treatment in 85 per cent of the cases and by the third day in 98 per cent The peripheral blood was also rapidly cleared of asexnal parasites which could not be seen beyond the second in 83 per cent and beyond the third day in 100 per cent The drug had little or no effect on gametocytes and relapses were less with the single dose No untoward symptom was encountered In view of the satisfactory response with a single dose Camoquin may prove a suitable remedy for mass treatment in rural areas

(ii) Atebrin (Mepacrine)

Atebrin —The work of Schulemann and his colleagues which culminated in the synthesis of plasmoquin was continued More than 1,200 compounds were prepared and eventually the drug originally called erion' and now known as atebrin was produced Chemically it is the dihydrochloride of an alkylamine acridine derivative and is a yellow powder with a bitter taste Its solubility in water [illegible]

[illegible]

Chopra and his co workers (1933) carefully tested this drug on the Indian strains of malaria and have concluded:—

(1) [illegible] peripheral circulation after 0 6 to 0 9 gm of the drug

(2) The sexual forms or gametocytes are more slowly acted upon than the asexual forms The gametocytes of the benign tertian and quartan types are readily destroyed The gametocytes of the malignant tertian type are not affected at all

(3) The drug is effective in doses of 0 1 gm three times a day the course lasting for five days making a total of 1.5 gm of the drug for the cure Recently a 7 to 10 days course is recommended in severe cases The drug can be given intravenously in doses of 0 1 gm to 0 3 gm dissolved in 3 to 9 ccm of distilled water respectively when the number of parasites in the peripheral blood is large

Soluble atebrine

Atebrin musonate is the soluble form of atebrin and was largely used in the epidemic in Ceylon It is an atebrin salt suitable for parenteral route 0 3 gm of atebrin being contained in 0 375 of the salt Hecht has shown that when atebrin is administered by mouth much of it is retained in the upper intestine, liver and bile and only the overflow goes to the peripheral circulation after these organs are saturated This exceptionally high concentration of atebrin is responsible for the manifestation of toxic symptoms. By injections the drug gets into the circulation quicker and gives response earlier Doses from 0 1 to 0 375 gm are given and a single injection often produces remarkable effects on the clinical symptoms, but recrudescence usually occurs in a few days Two similar injections on successive days, proved sufficient to control the temperature within 48 hours and in four days in all forms of benign tertian.

Combinations

Both quinine and atebrin have been combined with plasmoquin in preventing relapses and for prophylaxis

Atebrin and Plasmochin combinations—As atebrin only acts on the asexual forms of malignant tertian parasites it has been combined with plasmoquin A comparative study of the action of atebrin and atebrin plasmochin combination on Indian strains of malaria by Chopra and co workers (1936) showed that (1) in cases of benign tertian and quartan malaria the combination of the two drugs is not more effective than atebrin alone in so far as the time of disappearance of the parasites from the blood is concerned, (2) in the case of

disappearance from the peripheral circulation atebrin alone and atebrin plasmochin combination behave in the same way, (4) the relapse rate is lower in cases when the combination of the two drugs is used, (5) the combination of the two drugs is more toxic

It is therefore recommended that in those cases where crescents are present a 3 days course of plasmoquin 0 01 gm twice daily be given after the course of atebrin is completed The toxic effects are thus minimised Combination of atebrin and quinine have also been used Much work was done concerning the effectiveness and toxicity of mepacrine during the World War II Mepacrine is not uniformly distributed in blood and tissues but is rapidly taken up by the body cells The concentration in blood according to Hamilton Fairely (1945) is 2 2 micrograms per 100 ccm but it is likely that the drug absorbed by the cells also exerts antimalarial action In the army during the war doses of 0 1 gm twice daly for two days in the week were used with good results but 0 1 gm daily suppressed an attack under all conditions (physical exertion cold altitude etc) in volunteers artificially infected by mosquito bites If this dose was taken for 4 days in a week a few developed malaria To prevent the development of malignant tertian malaria it was necessary to give 0 1 gm daily for 28 days after the last infection

Prolonged use of mepacrine for periods as long as 18 months produced no toxic effects

Curative action —During World War II in cases of malaria with presence of parasites fever anæmia enlarged spleen etc 5 grains of quinine were given in doses of from 0 1 to 0 3 gm three times daily for three days The advantage of giving quinine at first is that it acts quickly and gives the patient relief from symptoms

(iii) Sulphonamide compounds

In view of the large number of bacterial infections which have been success ... it is not surprising that these drugs

(iv) Paludrine (No 4888)

ork has cles utoe

before the parasites be demonstrated in the blood Until recently the immediate fate of the sporozoites was uncertain, but it has now been shown that a period of development of the parasite occurs in the solid tissues and cells of the reticulo-endothelial cells of the vertebrate host, before the red cells are invaded, it is the duration of this tissue phase which constitutes the incubation period The development phase occuring during this period is the post sporozoite phase or the tissue phase (primary exo-erythrocytic phase) and the parasites at this time are called *cryptozoites*, or extra erythrocytic forms

After this period of incubation the parasites come out of the endothelial cells and begin their erythrocytic phase. They enter into the red blood corpuscles within which a generation of parasite is formed leading from the trophozoite form to the segmented forms The corpuscles containing the segmented forms (Schizonts) of parasites rupture ushering in the clinical picture and setting free the new merozoites to begin the next phase, It is possible that these merozoites are not all killed or partially destroyed In cases of relapse possibly the following cycle takes place —

The young merozoite on entering the endothelial cells continues its development as the secondary exo erythrocytic phase Parasites inside the endothelial cells of primary exo erythrocytic phase also continue their development into the stage of secondary exo erythrocytic phase After a course of time, the parasites [illegible]

of relapse

The conception of primary exo erythrocytic phase explains the enigma of incubation and of secondary exo-erythrocytic phase that of relapse and recrudescence.

The exo erythrocytic forms are known to occur in almost every type of avian malaria and are found in endothelial cells in the tissues They occur as a stage between the sporozoites introduction by the infected mosquito, and the parasites which eventually get within the erythrocytes, they may also persist through the time an infection lasts and serve as a reservoir from which parasites may be released to invade more blood corpuscles

Short and Garnham discovered the continued existence in monkey malaria of the exo erythrocytic forms in the liver after establishment of blood infection and after the parasites disappeared from the peripheral blood They suggest that this persistance of the exo-erythrocytic state plays an essential part in the maintenance of the infection over long periods and in the production of relapse.

That an exo erythrocytic form must occur in association with human malarial nfect [illegible] -mpts at transmission of human malaria, [illegible] from the fact that when human beings [illegible] iparum and P vivax the growth of P [illegible] the further development of P vivax, [illegible] e blood so long as the body is infected with *P fa ciparum*, an instance of interference, a phenomenon well known in connection with viruses

Subsequently Shortt Farnham, Covell and Shute (B M. J March 20 1948) have shown presence of pre erythrocytic stage of human malaria, *Plasmodium vivax*

In view of this there are three possible targets in the chemotherapy of malaria *namely the sporozoites* the tissue phase and the blood phase Clinical symptoms do not appear till the blood phase and therefore all efforts till recently were naturally *directed towards this phase* From this point of view quinine and [illegible] In all experimental [illegible] *in Roehls test* The [illegible] or the tissue phase preventing the parasite from appearing *in the blood was not attempted* For this purpose laboratory infection in chicks with *P gallinaceum* was established and a technique was evolved by which action on the sporozoite or the tissue phase could be tested Investigations were started with anilinopyromidine derivative and thousands of compounds were synthesized and tested To compound No 4888 the name of Paludrine was given Administered orally it is absorbed rapidly and almost completely, the peak levels are reached within three hours of administration Fall away in concentration is rapid although sufficient may remain after twelve hours to cause a build up if the drug is taken twice daily, this build up reaches its maxmum after four to six days (Maegraith Adams et al 1945) The concentration of 'Paludrine' in the red blood corpuscles is about four times that in the blood plasma.

Excretion is more rapid than mepacrine Even after a dosage of 0.5 gm. twice daily the blood concentration falls below assayable level within one week from cessation of the dosage and the drug cannot be detected in the urine after nine days Because of rapid excretion no ill effects have been reported following long continued use as a prophylactic

In animal experiments it has no adverse effects on blood pressure respiration or intestinal movement

In man even minor toxic side effects have not been observed except after the administration of comparatively large doses In a proportion of cases receiving 0 5 gm twice daily vomiting and epigastric discomfort have been reported In most instances the symptoms could be prevented if the drug were taken with a glass of water and they were usually only apparent during the first few days of the treatment Even when the treatment was continued for as long as 28 days and when the dose was increased to 0 75 gm given twice daily for a similar period no further toxic by effects were manifested (*Maegraith, Adams* et al 1945) A single dose of 1 gramme produced diarrhoea and haematuria but there was no evidence of *parenchymal damage to the kidney*

Curative.—In the treatment of malaria two courses of action may be adopted, either (*a*) clinical cure by which is meant reduction of the temperature to normal and control of the acute attack, or (*b*) radical cure that is to say, complete eradication of infection

Fairley et al *(1946) have shown that a single* dose is *sufficient to* end in attack of malaria and bring the temperature to normal Their results have been amplified and extended by trials in Britain and India.

It is desirable that for the clinical cure of all types of malaria a "single dose' of 0 3 gm (three tablets) should be given daily till symptoms are controlled

To obtain a radical cure a dose of 0 1 gm. (one tablet) three times daily for ten days should be given

Malignant tertian malar

In a short course of treatment it will not radically cure all cases of benign tertian malaria Some will relapse although the periods between relapses are longer after its use

Benign terti malaria.

It has been shown, however, that a dose of 0 1 gm to 0 3 gm twice weekly for six months at spaced intervals, after the acute attack has been controlled will hold off relapses indefinitely There are theoretical reasons for supposing that by this continued suppression, the persistent forms of the parasite in vivax malaria will be eradicated

Because of its ease of absorption and rapid effect when given by the mouth Paludrine has not been used to any great extent by the parenteral routes Doses of 0 1 gm however, have been given intravenously without demonstrable toxic effects and have been used successfully in the relief of cerebral malaria

Parenteral adm nistratio

Malarial Protection

Causal Prophylaxis—By causal prophylaxis is meant killing the parasite before it enters the red blood cells To achieve it a drug must kill either the sporo-
... will kill the
... omplete causal
... en at approxi-
... would give
complete protection against malignant tertian malaria

It has also a partial causal prophylactic action against benign tertian malaria, but dosage which might achieve complete causal prophylaxis would probably be impracticable

Clinical Prophylaxis—By clinical prophylaxis is meant inhibition of parasite ...

A once-weekly dose of 0 3 gm is only recommended when the administration of 0 1 gm twice weekly (at three or four day intervals) is inconvenient The twice-weekly treatment should be followed wherever possible because in addition to suppressing benign tertian malaria, it will give complete causal prophylaxis against malignant tertian malaria.

Gametocidal Effect—The drug is not gametocidal in man in the accepted meaning of the term but it prevents the development of the gametocyte in the gut of the vector mosquito This effect depen ...
a small quantity of the drug along with ...
Astonishingly small concentrations seem ...
has been receiving 0 1 gm of the drug t ...
mitting infection about a week later, although by this time the concentration of the drug in his blood is too low to be estimated by the available biochemical methods

(8) Cinchona Alkaloids Versus Synthetic Anti-Malarial Drugs

What is going to be the effect of the introduction of these powerful synthetic antimalarial drugs on the cinchona alkaloids? Are these old veterans going to be entirely replaced by the new comers? The Malaria Commission of the League of Nations pointed out that neither of the two groups, however intensive the treatment may be, is *therapia magna sterilisans* and their effect *in preventing* relapses is not marked They also have no true causal prophylactic action in all forms of malaria The synthetic drugs according to the Commission are not to be regarded as 'substitutes for quinine but as additional weapons for use in particular circumstances and for special purposes'

Quinine is an effective drug against malaria and its combination with mepacrine pamaquin and pentaquin is definitely advantageous Its sedative action on the central nervous system and heart is further a great asset in controlling certain symptoms of malaria such as headache, malaise general pains etc

This is probably the correct point of view The cinchona alkaloids have a very low degree of toxicity and can be used with impunity in the mass treatment of malaria and even self medication by the patient is without any danger [illegible]

[illegible]

under proper medical supervision [illegible] *[illegible]ditions toxic effects* are met with Unless paludrine has a low enough toxicity, the cinchona alkaloid will hold the field in the treatment of malaria among the masses generally, in this country

During the last few years it has been debated whether the cinchona plantations in this country should be exter[illegible] against *their extension* is that in [illegible] antimalarial drugs there will be no [illegible] writer has no hesitation in saying that unless paludrine is proved to have all qualities desired for the next 10 to 15 years we shall have to use the cinchona alkaloids in our struggle against malaria in India The cinchona plantations take 7 to 8 years to mature and if we wish to extend the treatment of malaria among the masses which is one of the chief methods of eliminating this disease it is very desirable that cinchona plantations should be extended till such time as an effective cheap and equally harmless synthetic drug is available which can be used for mass treatment of malaria without any special supervision

In India large scale and economic production should be taken in hand now that information is available regarding the species of cinchona which yield the highest percentage of the alkaloids and the best soil for cultivation

PART III

CHAPTER V

SPIRAL DISEASES

SYPHILIS PATHOLOGY AND CLINICAL ASPECTS ACQUIRED SYPHILIS NEURO-SYPHILIS, CONGENITAL SYPHILIS, TREATMENT OF ACQUIRED SYPHILIS CHANCES OF CURE TREATMENT OF EARLY SYPHILIS MODERN INTENSIVE THERAPY PENICILLIN IN TREATMENT OF SYPHILIS THERAPY OF LATE SYPHILIS—YAWS—THE RELAPSING FEVERS—RATBITE FEVER—OTHER SPIROCHAETAL DISEASES INFECTIOUS JAUNDICE (WEIL'S DISEASE), JAPANESE SEVEN DAYS FEVER, (NANUKAYAMI)—ARSENICAL COMPOUNDS PHARMACOLOGICAL ACTION, ARSENIC COMPOUNDS, MODES OF ADMINISTRATION, ORGANIC COMPOUNDS OF ARSENIC ATOXYL, TRYPARSAMIDE STOVARSAL (ACETARSONE), TREPARSOL ARSPHENAMINE, NEO-ARSPHENAMINE OXOPHENARSINE HYDROCHLORIDE (MAPHARSIDE) SULPHARSPHENAMINE THIOSARMINE TOXIC EFFECTS OF ARSENIC COMPOUNDS IMMEDIATE, EARLY AND LATE REACTIONS TREATMENT—BISMUTH AND ITS DERIVATIVES PHARMACOLOGICAL ACTION, THERAPEUTIC USES MODES OF ADMINISTRATION TOXIC EFFECTS TREATMENT, BISMUTH COMPOUNDS, SUMMARY—MERCURY AND ITS DERIVATIVES PHARMACOLOGICAL ACTION, THERAPEUTIC USES MERCURY IN SYPHILIS PROPHYLACTIC USES, MODES OF ADMINISTRATION, TOXIC EFFECTS, PREPARATIONS—IODIDES IN SYPHILIS

DISEASES CAUSED BY SPIRAL ORGANISMS

Spirochaetes are organisms which have flexible bodies. These organisms were placed by Schaudinn among the protozoa while other workers have refuted this and have placed them as being more closely related to bacteria—class *Schizomycetes*, order *Spirochaetales* Dobell considers that they belong to a special group of the *Protista* which he calls *Spirochaetoides* as they have characteristics common to both bacteria and protozoa Spirochaetes have no definite nucleus (as have protozoa), they reproduce by transverse binary fission into two equal forms, and have an anterior and posterior end There are no flagella but they have some inherent sinuous and rotating movements and power of motility The pathogenic spirochaetes are more flexible than bacteria They do not form spores, but granular forms have been observed and described as representing a stage in the life cycle of the organism, filtrates containing such granules have been shown to be infective, but it is possible that some flexible spiral forms may go through bacterial filters Infectivity of granular forms is therefore, still not proved Spirochaetes in the animal body are susceptible to the destructive action of compounds of antimony, arsenic, bismuth and mercury

Classification

Attempts to subdivide the members of this group have not been very successful The common spirochaetes of man and animals are given in the following table (Medical Protozoology, Das Gupta) —

Treponema	*recurrentis*	Man	Blood	Relapsing fever
"	*pallidum*	"	Tissues	Syphilis.
"	*pertenue*	"	"	Yaws
"	*carateum*	"	Skin	Pinta.
"	*vincenti*	"	{ Skin	? *Ulcus tropicum* (Naga sore)
			{ Throat	? Vincent's angina.
"	*dentium*	"	Mouth	——
"	*medium*	"	"	——
"	*buccalis*	"	"	——

Treponema macrodentium	Man	Mouth	—
" *mucosum*	"	"	—
" *eurygyrata*	"	Intestine	? Spirochaetal dysentery
" *stenogyrata*	"	"	—
" *intestinalis*	"	"	—
" *bronchiale*	"	Bronchi	Bronchitis
" *refringens*	"	Genitalia	—
" *gracile*	"	"	—
" *theileri*	Cattle	Blood	Relapsing fever
" *equi*	Horses	"	"
" *ovinum*	Sheep	"	"
" *suis*	Pigs	"	"
" *cuniculi*	Rabbits	Tissues	Rabbit syphilis
" *anserinum*	Geese Fowls Ducks	Blood " "	Relapsing fever " "
Leptospira icterohaemorrhagica	Man	*Blood*	Weil's disease *(Acute infective* jaundice)
Leptospira hebadomadis	"	"	Japanese seven-day fever
" *canicola*	Dog Man	" "	Stuttgart dog plague. Canicola fever
" *grippotyphosa*	Man	"	Swamp fever
Spirillum minus	"	"	Rat bite fever (Soduku)

T recurrentis and *T duttoni* which produce relapsing fever are now placed under genus *Borrelia*

The pathogenic spiral organisms of man may be classified as follows —

1 *The blood inhabiting spirochætes, viz* those of the relapsing fevers and *Spirillum minus*, the parasite of rat bite fever

2 The *Leptospira group* including the parasites of Weil s disease and Japanese seven-day fever

3. The *Treponema group* including the spirochætes of syphilis and yaws

4 *Vincent's spirochæte,* which together with the fusiform bacillus is responsible for Vincent s infection

[illegible]

be found In stained films the spirochætes show a very irregular appearance with widely open coils, twists and every possible variation in type.

T recurrentis passes through a Berkfeld filter and infected blood, diluted with ten parts of saline-citrate solution under fifty pounds pressure is infective to rats The filterability is attributed by some to a granule phase, while others have found definite spirochaetes in the filtrate. T. pallidum is said not to pass through this filter.

Spirillum minus, the cause of rat bite fever, is commonly met with in India. This organism is found in the blood of infected mice, rats or guinea pigs during the first two weeks and then becomes distributed in the connective tissues of the lips, nose, and tongue It has been found that about 3 per cent of house rats are carriers of the disease

The Leptospira group These organisms are characterised by the fact that the body consists of a spirally wound thread the spirals being so fine that unless careful inspection is made they are overlooked. Under the dark ground, the leptospira look like brilliantly refractile swimming pieces of rope. The two diseases due to leptospira infection in man are —(1) Weil's disease due to *L icterohæmorrhagica*, (2) Japanese seven-day fever due to *L hebdomadis*

Treponema pallidum The spirochæte of syphilis has essentially the same structure as the relapsing fever spirochætes, from which it differs only in being smaller and in having a larger number of coils for a given length These are essentially parasites of the tissues and of the lymphatic system and include the following species —(a) *Treponema pallidum*, the spirochæte of syphilis, (b) *Treponema pertenue*, the spirochæte of yaws, and (c) *Treponema cuniculi*, a spirochæte of the rabbit.

The discovery of the spirochæticidal power of arsenic and its derivatives marked the dawn of a new era in chemotherapy The researches of Ehrlich and many other renowned workers that followed him were directed primarily to fight the organism of syphilis i e, *T pallida* The success attained in this direction has done much towards solving the problem of spirochætal infections in its protean manifestations.

1. Syphilis

Although syphilis was not a very serious problem in India in the past, the two World Wars have increased both the incidence and the severity of this disease in this country It has therefore been described briefly below:—

(1) Pathology and Clinical Aspects

Historical

That syphilis, which formerly was a dreaded disease, which often led to the most [illegible]

are individually large and more destructive than in the secondary stage, and appear after a latent period lasting from a few months to many years after the subsidence of the secondary stage Tabes dorsalis and general paresis (G P I) are now generally regarded as manifestations of quarternary syphilis

Mode of infection

[illegible] e g, [illegible] or [illegible] earl[illegible] the [illegible] is infectious for animals chiefly in the primary and secondary stages but very rarely in the tertiary stage. That the infectivity of the blood usually dies out quickly after the first year is shown both by experimental and clinical evidence. Repeated transfusion to non syphilitic patients, from cases suffering from late manifestations of syphilis, does not produce infection in the recipients The semen has been shown to be infective very much longer.

Treponema macrodentium	Man	Mouth	—
" *mucosum*	"	"	—
" *eurygyrata*	"	Intestine	? Spirochaetal dysentery
" *stenogyrata*	"	"	—
" *intestinalis*	"	"	—
" *bronchiale*	"	Bronchi	Bronchitis.
refringens	"	Genitalia	—
gracile	"	"	—
" *theileri*	Cattle	Blood	Relapsing fever
" *equi*	Horses	"	"
" *ovinum*	Sheep	"	"
suis	Pigs	"	"
cuniculi	Rabbits	Tissues	Rabbit syphilis
" *anserinum*	Geese	Blood	Relapsing fever
	Fowls	"	"
	Ducks	"	"
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4 *Vincent's spirochæte* which together with the fusiform bacillus is responsible for Vincent's infection

The Relapsing fever spirochætes The spirochæte of relapsing fever was first described by Obermeier (1873) and was named *Spirochæta obermeieri* Since then a large number of different species of the relapsing fever spirochætes *e g* *T recurrentis* *T duttoni* *T* [illegible]

[illegible] be found In stained films the spirochætes show a very irregular appearance with widely open coils twists and every possible variation in type.

[illegible] blood, diluted with ten parts [illegible] to rats The filterability [illegible] und definite spirochaetes [illegible]

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1. Syphilis

Although syphilis was not a very serious problem in India in the past, the two World Wars have increased both the incidence and the severity of this disease in this country. It has therefore been described briefly below:—

(1) Pathology and Clinical Aspects

Historical

That syphilis, which formerly was a dreaded disease, which often led to the most [illegible]

Mode of infection

Infection occurs through the entry of the *Spirochæta pallida*, present in the discharges, e g, semen, saliva, or in the blood, either through a breach in the skin or mucous membranes or directly into the blood stream The organisms are present on the discharges in the early part of disease and transmit infection to others Experiments on rabbits show that the blood is infective from a week or earlier after inoculation, and in syphilis, the blood is infectious for animals chiefly in the primary and secondary stages but very rarely in the tertiary stage. That the infectivity of the blood usually dies out quickly after the first year is shown both by experimental and clinical evidence. Repeated transfusion to non syphilitic patients, from cases suffering from late manifestations of syphilis, does not produce infection in the recipients The semen has been shown to be infective very much longer

The commonest method of infection is through sexual intercourse and it has been estimated that only 8 or 9 per cent of the infections are extra genital The majority of *extra genital* chancres are found on the tongue and lips and next in frequency come the breast and nipple Syphilitic tissue excised 96 hours previously are infective to animals but d scharges become non virulent in a few hours Post mortem material 48 hours after *has produced infection T pallidum* is destroyed by drying and weak antiseptic solutions Low degress of heat (50°C) kill it *T pallidum* can bore its way rapidly through the cells of the body and this explain its power of reaching all parts of the body

The *Spirocl aeta pallida,* also known as *Spironema pallidum* or *Treponema pallidum* appears as a motile deadwhite delicate corkscrew shaped organisms with clear cut very regular coils Its length varies *from 4 to 14 its thickness* is 0.25 g the distance from the width of a red blood corpuscle.) It is best shown in discharges from *ation S pallida is indistinguishable*

Recently the unitarian theory of disease due to the spirochaete Treponema, has been propounded. It is believed that there is only one species T pallidum propagated both by venereal and non venereal routes. The forms of disease caused by this organism are characterized by early and late stages separated by a latent period with character stic pathological* response to treatment with heavy metals and pen cillin The name *Treponematosis'* is suggested for these conditions which includes all forms of yaws framboesia syphilis etc *Treponema* has been adopted as the generic name for the micros *copic paras te*

The lymphatic glands draining the area

In the secondary stage the skin lesions are usually macular or papular and there may be *increase or decrease of pigmentation in the affected areas Lesions of the mucosa of* the mouth fauces and anal canal are similar to those in the skin.

Tertiary skin lesions consist of granulomas composed of collections of epithelial cells plasma cells and numerous lymphocytes The centre of the lesion becomes necrosed and ulceration results In the subcutaneous and submucous tissues muscles bones and testes tertiary lesions are discrete or diffuse and there is tendency to degeneration and eventual fibrosis

It is well known that syphilis is generally a milder d sease in females Sp rochaetes though common in the testes of old syphilitics are very rare in the ovaries *It has been* suggested that possibly the female sex hormones are responsible for this In warm climates syphilis is also a comparatively milder d sease Card ovascular and quarternary nervous manifestations are not so frequently met with *in Ind a as in Western countries*

The most valuable test for early syphilis is the microscop c examination of the juice of the lesion contain ng as little blood as possible, for *S pallida* under the dark ground illumination Serological tests are divided into the complement fixation or Wassermann test, and the flocculation or precipitin tests In addit on to these tests the cerebrospinal fluid is usually tested for increase of globulin, increase of cells (above 5 cells per cmm being generally considered pathological) and for one of the colloidal reactions *e g* gold benzoin or mastic

It is generally agreed by most authorities in India, that a very large number of false positive Kahn and Wasserman reactions are met with in Indian patients hospitalized for a variety of trop cal diseases Such false pos tive reactions frequently become negative without any anti syphilitic treatment *and are most frequently encountered in malaria* kala azar leprosy yaws trypanosomiasis p nta and relapsing fever

(i) Acquired syphilis

1 *Primary stage* —The incubation period varies from 10 to 90 days or longer the most common being from 3 to 4 weeks *The longer incubation periods may be due to* unsuccessful attempts at prophylaxis by local disinfection or to the taking of antisyphilitic drugs by mouth or by the parenteral route The primary sore known as a chancre then appears Chancres are *generally single but may be multiple* The commonest site in men

is the coronal sulcus other sites being the prepuce, frenum urinary meatus, or dorsum of the penis. In the female, the primary sore is often found in hidden situations *e g*, on the labia, clitoris, mouth of urethra, posterior commissure, remains of the hymen and the os uteri. It gives rise to little or no discomfort

Diagnosis

The blood serum gives a positive Wassermann and positive flocculation tests in more than 50 per cent of cases, 10 to 14 days after the appearance of the primary sore. About 4 to 6 weeks later, almost 100 per cent of cases are positive. The cerebrospinal fluid may sometime show changes even before the serum is positive.

Certainty and speed
the outlook is best wl
Diagnosis of primary s
serum test is positive
appearance The most
rubbery induration of t
of the lesion Marked
active inflammation is often a very valuable sign.

The commonest non syphilitic lesions on the genital area from which syphilitic chancres must be distinguished are chancroid or soft chancre herpes vesicles, balanitis, granuloma venereum, the primary lesion of lyphogranuloma inguinale, gonorrheal sores and malignant disease.

Secondary stag

2. *Secondary stage* —This stage is one of generalization of external lesions and is

Skin lesions

The first rash may appear overnight, distributed all over the trunk and limbs, or it may be confined to one part from which it may or may not spread to the limbs or head. The parts subject to irritation are often more affected. The macular or reseolar syphilide varying in t red, later the roseola of normal

The lenticulo papular eruption usually follows the roseola, but it may be the first secondary eruption It appears as dome shaped papules, which vary in size from a lentil to a pea *S pallida* can almost always be found in the serum which oozes from the papules Degeneration of the papules may result in scaling and the rash may then be mistaken for psoriasis In neglected and debilitated patients the papules may become pustular and the whole body may be covered with crusts A more severe degree results in syphilitic rupia. Loss of hair (syphilitic alopecia) occurs in a large proportion of cases of secondary syphilis

Mucous memb

Secondary lesions of the mucous membrane are essentially papular the centre of the lesion is occupied by a thin white pellicle and round this is a raised red sharply defined producing the classical ers are on the mucous ula, and the soft palate labia, vagina cervix us patches are generally

Gummata

3 *Tertiary stage* —Lesions of the skin occur as (1) tubero-serpiginous syphil des (a central nodule surrounded by a ring of similar nodules) with a tendency to degeneration and scaling and eventual cicatrization, or in formation of small ulcers. (2) The single gummatous ulcer originates in the subcutaneous tissues, muscle, or bone, as round elastic painless swellings which merge with the skin, breaking down in the centre, they give rise to the classical tertiary ulcers, with base covered with a washleather slough and punched-out indurated edge.

A diffuse interstitial myositis may affect any muscle, particularly *one of the flexors*, individual gummata may form in one or more muscles and may break through to the skin, or retrogress and lead to shrinkage of the whole muscle, which may calcify or even ossify

ppear on any bone as a smooth swelling connected with *ribs, sternum, cranium and tibias* are commonly affec ification and remain as an ivory hard boss on the bone, ... The centre of the swelling may break and result in a funnel shaped gummatous ulcer, with a bare bone base A diffuse periostitis is far commoner in congenital syphilis producing sabre scabbard tibia

Gummatous infiltration of the nasal bones leading to necrosis and offensive discharge is important, and unless promptly treated, may result in serious deformity Eventually the bridge of the nose may be destroyed and fall in, and the palate may be perforated.

Gummatous arthritis which is painless, most commonly involves the knee, which is uniformly enlarged, there is little or no muscular wasting round the joint Gummatous nodules may be felt in the synovial membrane

Charcots joints may occur in tabes, and are diagnostic of the pre ataxic stage. The joint attracts attention as it suddenly becomes distended with fluid, without pain or inflammation, or may suddenly give way or become dislocated without apparent cause.

Tertiary ... diffuse
but the two ...
and heavy,
as smooth ... ay
commonly occurs and early tapping may become n
involved

Leucoplakia of the tongue and cheek is common in the later stages of syphilis Interstitial glossitis occurs, the tongue becomes smooth, red and glazed Gumma of a tonsil may appear

...lar

In western countries, syphilis is responsible for 10 to 15 per cent of *all cardiovascular* disease, and this type is said to be responsible for about 30 per cent of all deaths from syphilis The incidence is very much lower in females than in males. In India, however, cardiovascular lesions are rarely encountered, even in the comparatively temperate regions *of the Punjab and Kashmir*

(ii) Neuro-syphilis

Syphilis is one of the common causes of organic disease of the central nervous system ... involvement of the central nervous system ... d vessels may be involved *early* ... vous parenchyma such as general ... earlier than 14 to 15 years after ... may not develop and

Harrison has classified neurosyphilis into —

1 *Intracranial syphilis*

(*a*) The brain substance is affected, gummata form and general paralysis of the insane is the result.

(*b*) The meninges are affected producing cerebral meningitis

(*c*) The blood vessels are affected producing cerebral vascular syphilis

2 *Spinal Neurosyphilis*

(*a*) The spinal cord tissue is affected producing tabes dorsalis progressive muscular atrophy, Erb s syphilitic spastic paraplegia

(*b*) The spinal meninges and interstitial elements of spinal cord are affected, gummata form producing acute syphilitic transverse myelitis, subacute and chronic syphilitic meningo-myelitis.

(*c*) When blood vessels are affected spinal vascular syphilis occurs

Neurosyphilis may occur in congenital syphilis resulting in mental deficiency infantile hemiplegia, juvenile tabes dorsalis.

General paralysis of the insane

General paralysis The disease usually begins between 8 to 20 years after the infection and is seen in 10 per cent cases of neurosyphilis in Western countries It may occur in adolescence as a result of congenital syphilis

Mental symptoms Mental changes which may take the form of either dementia, or delusions of grandeur type, are the first to appear Later the memory fails and there remains little mental activity the patient lying regardless of his surroundings

Speech defects Tremors are amongst the earliest physical signs They start in the tongue and spread to hands and feet The speech is jerky and slurring as also is writing Mental deficiency further affects spoken and written speech Pupillary abnormalities are very common, unequal and irregular pupils are the usual phenomenon, complete Argyll Robertson pupil being rather uncommon.

Paresis The pyramidal tracts are involved leading to extensor plantar reflex and exaggerated deep reflexes Attacks of congestive hemiplegia or monoplegia occur with some recovery but ultimately lead to more and more weakness The control of urinary bladder and defaecation are also lost Sexual impotence is also present.

Sometimes tabes dorsalis and general paralysis of insane may occur together and then a mixture of the features of both the disease may be seen. Mental changes are as a rule mild in these cases

C.S.F reaction The cerebrospinal fluid and the blood give positive Wassermann reaction and Lange s colloidal gold test shows paretic type of curve Leucocytosis occurs and proteins are increased in the cerebrospinal fluid.

Tabes Dorsalis —It is the commonest form of nervous syphilis due to degeneration of posterior columns of the spinal cord. There is a large variety of symptoms the commonest features are lightning pains.

Sensory disturbances Objective d sturbances of sensation loss of tendon reflexes, incoord nation disturbance of pupillary reflexes in particular the Argyll Robertson pupil and impairment of bladder control are frequent. Less common are visceral crises (acute disturbance of motility of certain viscera) gastric crises and less commonly rectal and vesical changes in joints (Charcot's disease of joints) perforating ulcers of skin.

Visceral crises

Syphilitic progressive muscular atrophy —The condition closely resembles muscular atrophies of any other origin The lesion is a degeneration of the anterior horn cells being most pronounced in the cervical region. The atrophy is seen to start in the upper limbs and there may be present some sensory symptoms of tabetic origin. The lower limbs often show spastic paralysis. The condition is steadily progressive

Acute syphilitic transverse myelitis —This condition is characterized by dramatic onset of complete paralysis of both the lower limbs accompanied by paralysis of bladder and rectum, following within six to forty eight hours of onset of pain around the waist. The usual site of the lesion is the eighth sp nal segment, where over one or two segments, there is intense infiltration with small round cells.

(iii) Congenital syphilis

Incidence of congenital syphilis. It is during the first half of pregnancy that syphilis is usually transferred to the fœtus, and adequate treatment of the mother before this usually prevents foetal infection. The classical sequence in an infected woman is first a series of miscarriages then still-births at term then live infants showing signs of the disease at birth, and lastly infants

who appear healthy at birth but who develop signs of syphilis at various ages *from one month to many years* Healthy infants may alternate with syphilitic ones It is the opinion of many eminent pediatricians that congenital syphilis is a comparitively rare disease, inspite of the frequency of the infection among parents

The great majority of syphilitic infants born alive show signs of the disease in the *first year* The infants blood at birth reflects the condition of the mother's blood and may give positive serum reactions even though the infant be not infected

One of the earliest manifestation is wasting or marasmus and anaemia Rashes of the skin and mucous membranes are common and appear about one month after birth. The *macules are most abundant on the napkin area* around the mouth and nose, on the palms and soles and at the mucocutaneous margins Ulcerative fissures may form leaving radiating scars which are of great help in diagnosis

The hair of the scalp may be shed extensively especially over the back and sides, and *loss of the eyebrows is highly suggestive of syphilis*

The mouth may show mucous patches and later in life, perforation of the palate may occur There may be leucoplakia of the tongue and the fauces may be ulcerated A chronic nasal catarrh popularly known as 'snuffles' is common and this results in *the well known saddle nose caused by the falling in of nasal arch Involvement of the* larynx produces the hoarse cry which together with the snuffles is characteristic.

Condylomata round about the anal region are not uncommon and are due to neglect of treatment in long standing cases

Th
rise to
areas
behind
tion a
limbs
are tender and enlarged and an apparent paralysis is often present This is due to pain and the child may scream if the limbs are handled The radiographic appearances are diagnostic

Symmetrical painless synovitis may appear in the knee joints at about the age of six years producing what are termed as Cluttons Joints'

The permanent teeth may show characteristic changes the upper and central incisors being most commonly affected These teeth are spaced out and have wider bases than cutting edges The cutting edges are rounded off and the centre of the edge is occupied ... Moon's teeth are dome shaped first ... llen together They ... rmanent teeth only

Eye affections are responsible for a large proportion of blindness in infancy Choroiditis and iritis often occur in the early months Interstitial keratitis is common after the first year The cornea gradually becomes opaque in a patchy manner and after some time *inspite of energetic* treatment the other cornea becomes similarly affected The opacities may become vascularized and a pink patch the classical 'salmon patch' is produced Later the cornea may start bulging or may become ulcerated

Otitis media may occur in connection with the snuffles The discharge is very infective and the whole middle ear and labyrinth may be destroyed and the child become a deaf mute.

The spleen is frequently enlarged. The liver may be considerably *enlarged* with a diffuse gummatous hepatitis and there may be slight jaundice Paroxysmal hæmoglobinuria is occasionally met with

A syphilitic orchitis causing a painless enlargement of the testis is fairly *commonly met* with

(2) Treatment of Acquired Syphilis

In America the interests of individual who suffers from it are considered less important than the community in which he lives and threatens to infect Short courses of *intensive* therapy have been recently devised to get the disease quickly under control but these carry a high mortality rate On the other hand if treatment lasts a long time, many patients do not complete the treatment and

remain a source of danger to the community A middle course would appear to be the best The old conservative methods of treatment and those introduced during recent years have been briefly described in the following pages —

Importance of early treatment

[illegible] the first [illegible] and adequate treat[illegible]

essential Most syphilitic infections are transmitted by persons during the first two years of their infection The maximum effort in the treatment of syphilis should be in the early stages to control infectiousness and to prevent development of the destructive lesions of late syphilis, and of syphilis in pregnancy to prevent congenital syphilis

Patients should never be treated merely on the basis of suspicion of syphilis The diagnosis should be supported by demonstration of the Treponemes or positive serological reactions supplemented by evaluation of physical signs

(i) Chances of cure

Cure of syphilis is usually meant to imply that the patient becomes and remains symptomatically well for a lifetime that he is incapable of transmitting the infection to others and that the blood and spinal fluid become and remain serologically negative.

Biological cure

Biological cure implies complete eradication of treponemes and co-existence of symptomatic and serological cure It can be most readily attained if treatment is begun during the first six months of infection

Serological cure

Serological cure means only that the blood and spinal fluids become and remain negative, it does not necessarily imply biological or symptomatic cure Symptomatic cure means that the patient becomes and remains well and non infectious as far as syphilis is concerned, for the rest of his life even though the serological reactions do not remain negative

Spontaneous cure

Without treatment, 30 per cent of patients with early syphilis may be expected to develop spontaneous cure, 30 per cent develop latent syphilis 15 per cent develop benign late syphilis and 25 per cent develop serious late syphilis

Influence of early treatment on cure rate

Proper treatm[illegible] In serone gative primary sy[illegible] attained In seropositive prima[illegible] ries from 70 to 95 per cent I[illegible] benign late syphilis the probability of symptomatic cure ranges from 60 to 95 per cent and of serological cure 30 to 40 per cent In simple aortitis symptomatic cure occurs in 70 to 80 per cent with serological cure in 30 to 40 per cent When aortic aneurysm is present arrest of progression of the lesion may be attained

In syphilis of the central nervous system biological cure is not to be anticipated In early involvement of the nervous system symptomatic cure occurs in 70 to 90 per cent and serological cure in 85 to 95 per cent. In diffuse, late central nervous system syphilis symptomatic cure ensues in 60 to 80 per cent and serological cure in 30 to 40 per cent In tabes dorsalis and general paresis the best to be hoped for is symptomatic cure.

Early syphilis

The term 'early syphilis' embraces all forms of the disease developing within the first four years after infection It includes the primary lesion and secondary lesions such as rash on the skin and mucous membranes mucous patches and syphilitic warts. Coincident with these lesions there are lesions in deeper structures including the liver, spleen, heart and brain

Late syphilis includes all types of the disease occuring more than four years after infection Its manifestations embrace those forms of the disease known as tertiary syphilis. The principal lesions are gummas of the skin mucous membranes and organs hepatic syphilis neurosyphilis cardiovascular syphilis and syphilis of the bones

(ii) Treatment of early syphilis

The standard conservative prolonged treatment routines with alternate administration of blocks of arsenicals and bismuth are well adopted to treatment of early syphilis Stokes et al commenting on the official long term system conclude that it is effective and will achieve all that the newer shortened systems will and with a very much greater margin of safety They further add that the conservative systems are still the back bone of modern practice

The alternating blocking method consists of alternating courses of neoarsphenamine or allied preparations and courses of bismuth The first block consists of a suitable arsenical such as neoarsphenamine sulpharsphenamine or mapharside ten to twelve injections in 8 to 10 weeks and following this with bismuth for six weeks.

The overlap block method shown in the table below is a modification of the *alternating block method is somewhat more intensive and is preferred by many* clinicians Alternating blocks of mapharside and bismuth are given as in the preceding method but the arsenical and bismuth are given concurrently for 2 or 3 weeks at the end of each course

Treatment of early syphilis Standard Long time Method

Time in Weeks		
0	*week 0 to 10*	
	Neoarsphenamine	
5	or Mapharside	
10	10 weekly injections I V	
		weeks 8 to 18
15		Bismuth
		10 weekly injections I M
20	*weeks 16 to 26*	
	Neoarsphenamine	
25	or Mapharside	
30	10 weekly injections I V	
		weeks 24 to 36
35		Bismuth
		12 weekly injections I M
40	*weeks 34 to 44*	
	Neoarsphenamine	
45	or Mapharside	
50	*10 weekly injections* I V	
		weeks 42 to 58
55		Bismuth
		16 weekly injections I.M
60	*weeks 56 to 66*	
	Neoarsphenamine	
65	or Mapharside	
70	10 weekly injections I V	
		weeks 64 to 80
75		Bismuth
80		16 weekly injections I M

Alternating therapy is then continued with alternate overlapping blocks of 10 weekly injections of arsenicals, and 16 weekly injections of bismuth, and is terminated with a course of bismuth

Potassium Iodide may be given concurrently with each course of bismuth injections but its use has been abandoned by many syphilologists ,With the conservative routine of syphilo-therapy, the fatality rate is less has 1 in 3000

... ve plan are ... Maphar- ... be used in ...

Bismuth injections in the above course are given in doses of 0 2 gm of bismuth metal weekly

The superiority of the continuous treatment plan, over the older schemes of interrupted therapy, particularly in early syphilis, is no longer in doubt It is now generally admitted that the continuous treatment of early syphilis is so far superior to any intermittent or irregular system as to leave no room for comparison In early active syphilis, all conservative routines call for at least 30 injections of arsenicals and from 30 to 36 injections of bismuth

With any long term plan for treatment of early syphilis, the average patient should be seronegative by the 16th week of therapy If the blood still remains positive at the 24th week of treatment, the spinal fluid serology should be examined If after the 26th week of treatment, weak positive serological reactions appear among negative blood tests, infectious relapse or neurosyphilis should be suspected

(iii) Modern intensive therapy

These methods are coming into increasing use, and are most suitable for ... previous anti syphilitic ... general clinical and ... tlined by Turner and ... le (Eagle and Hogan ... ience has accumulated ... U S Army Plan for ... iot recommended for ... use, except where physicians feel that patients will otherwise fail to complete the standard fiftytwo to eighty weeks course of arsenicals and bismuth now in general use.

The U S Army Plan course extends over a period of 26 weeks Neoar sphe... ten ... inje... are ... weel ... during weeks 16 to 21 and finally given again during weeks 21 to 26

The U S Ar Plan

This plan calls for forty ... or of mapharside in doses of ... the 26 weeks Results are pr... risk to the patient is only sli... this method of treatment ran... safety being 8 as compared with a margin of 10 for standard therapy

The twelve week Eagle Plan extends over twelve weeks during which period a total of 36 injections of neoarsphenamine or mapharside are required, 3 injections being given each week *In addition to arsenicals, weekly injections* of bismuth salicylate (0 2 gm equivalent to 0 13 gm of bismuth metal) are given This undoubtedly helps in producing a cure. Three weekly injections of mapharside alone produced fewer cures but combined with bismuth more than *80 per cent of patients were cured in 9 to 12 weeks* Encephalopathy, dermatitis jaundice and fall in polymorphonuclear leucocytes rarely occur with intensive therapy Results are said to be good in seronegative and seropositive primary syphilis and in secondary syphilis However as the curative dose of the arsenical is given in a much shorter time than by other methods of ambulant therapy *the risk of serious ill effects is increased* *The estimated mortality with the* Eagle Plan is 1 in 400 to 1 in 1000 Thus, this plan should only be used only with full recognition of its potential danger to the patient

Massive Dose Arsenotherapy Intensive therapy of early syphilis with heroic doses of arsenica [illegible] by the Mt Sinai Hosp [illegible] 1939) It consists of [illegible] of 5 per cent glucose solution, by slow intravenous drip (3 cc per minute) over an eight to twelve hour period daily, for five days A total dose of 1 000 to 1,200 mgm or the equivalent of twenty standard doses of mapharside, is thus given over a period of five days

Modifications of intensive drip therapy of early syphilis, using multiple injections by the syringe, have been tried They call for a total dosage of [illegible] ix to twenty days, the average period [illegible] tially of giving an injection of 60 to [illegible] and repeating this every day until a total of 1 200 mgm has been given [illegible] S Army adapted a 20-day treatment in which 1 0 mgm of mapharside was given per kilo body weight *daily together* with 8 doses of bismuth salicylate In some patients treatment had to be discontinued because reactions occured commonest being fever from 6th to 15th day of treatment, jaundice and encephalopathy rarely occured

Data at present available on the risk to patients receiving intensive chemotherapy within a one to twelve day period reveal that the mortality is in the neighbourhood of 1 in every 200 patients treated This death rate even under expert management, emphasizes *the hazard of ultra intensive arsenotherapy in* general practice

Combination [illegible] The heat [illegible] for treponema has been shown by *the fac* [illegible] temperature of 4[illegible] (2) by injectiong [illegible] application of he[illegible] especially of the severe type

Artificial fever therapy has been considered better than malaria and vaccine therapy but it requires an expensive apparatus The advantage is that the temperature can be regulated its duration of application can be varied as desired The author has however used malaria therapy successfully in India in a number of cases of neurosyphilis without any untoward effects

Artificial fever therapy is not without risk to the patient and his condition has to be carefully watched during its application Treatment should be stopped if the systolic pressure falls below 100 or pulse rate goes over 150 and respiration rate over 50 per minute, or there is extreme *restlessness* vomiting or coma.

Fever therapy has been combined with injections of arsenic and bismuth but has not been found satisfactory in the treatment of early syphilis. Before each application the patient is given an intramuscular injections of bismuth salicylate (4 grains) mapharside in doses of 60 to 100 mgm is given an hour and a half after the fever (105 to 106°F) has been produced which should be continued for ten hours

(iv) Penicillin in the treatment of syphilis

Four different types of penicillins have been isolated F G X & K. Of these the most active against syphilis is G, K is least efficacious because it is rapidly excreted. Penicillin is undoubtedly effective against primary and secondary

Penicillin G in Syphilis

be just as effective as arsenicals and bismuth compounds in the prevention of women. It is also effective in healing mucous membrane. It cures cases of bismuth compounds but is ineffective particularly useful in cases showing sensitiveness to organic arsenicals. Herxheimer's reactions undoubtedly occur with penicillin but these can be prevented by regulating the dose in the early stages of the treatment, and often are not serious

The disadvantages of penicillin are the need of frequent intramuscular injections (every 3 to 4 hours) but this may be overcome by giving 3 to 6 hundred thousand units of the drug daily in peanut oil and bees wax or aqueous solutions mixed with vegetable oils but weekly injections like those of arsenicals and bismuth are not yet possible. Perhaps suitable compounds for this and for oral administration will be discovered in the near future which will make treatment very convenient

Penicillin in early syphilis (Primary & Secondary) The quick control of

Different forms of treatment with varying doses and duration have been tried but the optimum dosage has not been definitely determined. As mere healing of the lesions is no criterion on the basis of serological and clinical relapses, a total dosage of a minimum of 2 400 000 units by intermittent intramuscular injections is considered effective (300 000 units daily for 8 days). This should be combined with daily intravenous injections of 40 to 60 mgm of mapharside. The two drugs undoubtedly have a synergistic effect

Methods adopted for penicillin treatment are —

(1) 60 injections of 40 000 units every four hours in ten days (2) 300 000 units in peanut oil or bees wax daily for 8 days 40 mgm of mapharside are also given in both (1 & 2) intravenously (3) 600 000 units in peanut oil and bees wax once a day for 8 days

Methods

The patient is carefully observed *for 2 to 3 months* weekly clinical examinations being made, serum and cerebro spinal fluid are examined at the end of this period In sero negative primary cases one course is sufficient but *in seropositive* cases one or more courses with or without mapharside are recommended After this serologic and clinical examinations should be made twice a year for five years If after 2 to 4 months of treatment there is clinical relapse or serum is positive it is no use giving penicillin treatment but treatment with arsenicals and bismuth should be given If coincident gonorrhœa is present penicillin may mask or delay development of chancre In such cases the patient should be kept under prolonged observation (Kolmer 1947)

Ambulatory treatment The use of penicillin in the treatment of syphilis required hospitalisation of the patient for 8 days As this is often inconvenient an ambulatory method was devised by Lloyd Jones and Maitland (1945) They give single daily intravenous injections of penicillin for 8 days the total dose given being 2 4 to 5 0 million units The relapse rate with this treatment was 4 0 per cent

The I ... ly used penicillin for the treatment of ... itients have been treated with various s... st method so far employed is the combination of 5 injections of oxyphenarsine hydrochloride (mapharside) 1,200 000 units of penicillin and 3 injections of a bismuth preparation given over a period of 10 days

Another system that is at present extensively employed is to give as soon as the diagnosis of syphilis is made four injections of 0 04 gm of mapharside on 4 *consequtive* days On the 5th day penicillin treatment is started and 40 000 units are given every 3 hours for 8 days (total 2 400 000 units) On the last day of the penicillin course treatment with bismuth salicylate in doses of 0 1 gm is started and ten injections are given at the rate of one every fifth day

The blood serology of patients who on the average from sixty to one hundre... ment of treatment Patients should be first year with clinical inspections and tests In the absence of clinical manif... falling to or towards seronegativity On the other hand the absence of quantitative serological response the presence of serological relapse as indicated by a rising titre or the appearance of new clinical manifestations is an indication for retreatment The patients spinal fluid should be tested six months after the completion of penicillin therapy If progress during the first year after treatment has been uneventful and sero negativity achieved the patient may be checked during the second year every three months Continued and prolonged observation for a minimum of five years is desirable If relapse occurs one may treat the patient again with penicillin utilizing for the second course a total dose at least twice that originally administered and combining with the second course a minimum of six injections of mapharside

On comparison of the results of various rapid systems of treatment the results favour penicillin only in the fewer number of reactions it produces The ... multiple injection technique ... ve a lower rate of failures ... considerably higher This seriously minimizes the practical value of the methods

The value of penicillin by the oral route, and the daily injections of 30 000 ... esent ... may ... one injection in a day necessary, for several weeks instead of one injection every 3 hours for 8 or 10 days

Penicillin in prevention of congenital syphilis

... month of pregnancy Complications are usually not encountered In the treatment of congenital syphilitic children however, penicillin has not so far proved so highly efficacious The benign manifestations such as periostitis or cutaneous gummas respond rapidly but interstitial keratitis had proved resistant to penicillin therapy

(v) Therapy of late syphilis

Under the term late syphilis are included latent syphilis visceral syphilis, neurosyphilis (including tabes dorsalis & paresis) and also cases of syphilis resistant to treatment

In late syphilis continuous treatment is desirable but not essential. Heavy metals are given over a long period of time Bismuth and iodides should precede arsenicals for four to ten weeks A suggested plan for the treatment of late syphilis by the conservative long term method is given below —

Week	*Arsenical*	*Week*	*Bismuth*	*Iodide*
0-4	—	0-6	6 weekly injections I M	Daily by mouth
4-12	6 weekly injections I V	6-10	—	—
12 16	—	10-18	8 weekly injections I M	Daily by mouth
16-26	10 weekly injections I V	18 24	—	—
26-34	—	24-36	12 weekly injections I M	Daily by mouth
34-44	10 weekly injections I V	36-42	—	—
44-72	—	42 54	12 weekly injections I M	Daily by mouth
72-82	10 weekly injections I V	54-62	—	—
		62 74	12 weekly injections I.M	Daily by mouth
		74-80	—	—
		80-96	16 weekly injections I.M	Daily by mouth

Due to the probability of cardiovascular and visceral involvement in late syphilis reactions must be avoided and cautious use of arsenicals is essential To avoid therapeutic shock and therapeutic paradox, therapy in late syphilis should always begin with bismuth and iodides A rest period of eight to ten weeks after one year of continuous treatment probably does no harm in late syphilis, but many syphilologists prefer continuous therapy

The Co operative clinical group of U S A 's (Stokes et al 1943) experience indicates that three courses of eight injections each of an effective arsenical such as neoarsphenamine or mapharside, give in alternation with 10 injections of bismuth, without overlap and with continuity extending only through the arsenical phase, constitute an adequate beginning Continuous treatment with arsenicals and bismuth is then followed by intermittent and prolonged treatment with bismuth alone, which should total including the three ten injection bismuth courses given with the arsenical phase, not less than sixty weeks of bismuth therapy

Semi intensive therap
The 26 week system used l
by them for treatment of
to be no reason why it
this phase of arseno therapy have been under way for some time but it is too early for any conclusions

Penicillin in late syphilis—The response of the late cutaneous manifestations of syphilis to penicillin therapy has been so rapid and remarkable that, although *a considerable period must elapse before its ultimate effect on tertiary syphilis* can be evaluated with accuracy, it has been recommended by eminent venereologists that with the exception of gross cardio vascular disease, all late cases should be given the benefit of penicillin therapy, in addition to whatever other treatment is necessary The risk of a Herxheimer reaction in late syphilis, however makes it necessary that therapy should in all cases commence very cautiously and 6 to 10 injections of bismuth with concurrent iodides by mouth every 4 or 5 days should always precede penicillin or even arsenicals The dosage of penicillin employed should total from two to four million units given 3 hourly over a period of 8 days

It is not known whether penicillin penetrates into the syphilitic lesions as well or better than arsenicals and bismuth compounds or whether clinical and serologic improvement is more or less readily produced or whether a combination of the two is more effective than penicillin alone Kolmer (1947) from his vast experience has suggested the following plans of treatment —

(1) I8 ... tion
every four ... ion
with five ... and
five doses ... 000
units of p ... ays
combined ... wo
months an ... so
that at least four courses are given in chronic latent syphilis and 4 to 6 courses in c onic symptomatic syphilis *unless otherwise indicated by serologic and spinal fluid examinations*

Cases resistant to arsenicals and bismuth generally respond to 60 doses of 40 000 units every 3 or 4 hours In sero-resistant cases there is probably a persistent treatment resistant focus (Kolmer) in the body and penicillin has not proved effective in these cases. Optic neuritis has improved with doses of 2 to 4 million units and progress of primary optic atrophy has been checked In latent syphilis penicillin is an excellent substitute for arsenical and bismuth compounds *As many as a hundred injections of 40 000 units have been* given with improvement in serologic reactions

Penicillin is well borne in pregnancy when administered to infected pregnant women in adequate doses (1,200 000 to 2,400 000 units intramuscularly), normal infants are born in more than 90 per cent after this treatment (arsenicals also do thus) The drug is therefore transmitted to foetus through the placenta. Cases of early congenital syphilis also improve under penicillin treatment and about 50 per cent become sero-negative

Prophylaxis of syphilis Prophylaxis in man with a single dose of penicillin however large, should never be tried as it is likely to suppress and not eradicate the disease The patient is thus placed in a very unfortunate position and uncertainty may persist for years If prophylaxis is to be given at least 20 intramuscular injections of 40 000 units in peanut oil and wax daily for 3 or 4 days in succession should be given

Penicillin in Neurosyphilis—Dramatic improvement has been reported in both the clinical condition and the cerebrospinal fluid in acute meningo-vascular syphilis though there is a risk of severe Herxheimer reactions such as acute transverse myelitis if preparatory preparation with bismuth injections is not done In tabes dorsalis the progress of primary optic atrophy is arrested and the cerebrospinal fluid improves There is also some improvement in other symptoms such as lightening pains

In dementia paralytica the drug should be used in combination with arsenicals bismuth or fever therapy Reports of results are conflicting but it is generally agreed that some improvement occurs in the spinal fluid of more than 50 per cent of the cases treated.

In asymptomatic neurosyphilis the results are excellent, the spinal fluids becoming normal in the majority of cases treated with penicillin alone Preparatory bismuth treatment should however always be given, and it is advisable to supplement the treatment with arsenicals

2. Yaws

Yaws or framboesia is an infectious contagious tropical disease of non venereal origin, it is characterised by an initial cutaneous papillary lesion the 'mother yaw" and is followed b[illegible]
tion of the skin, sometime late [illegible]
occur It is caused by the [illegible]
indistinguishable from *T pallidum* of *syphilis* The organism is present in large numbers in discharges from lesions

Yaws essentially occurs in the tropics and it does not spread when introduced to [illegible]

[illegible]

Various views are held on the relationship of yaws to syphilis but perhaps most conservative view in this connection is that the virus of yaws is a modified virus of syphilis a less virulent one producing a disease which has been modified through the epidermis in tropical peoples, and by their habits and the climate and conditions under which they live Syphilitic lesions occur in the skin bones, muscles, the nervous system and the cardiovascular system The lesions of yaws are confined to the skin and later to the bones and the disease is not congenital. There is much convincing evidence that an individual who has acquired immunity to yaws is also immune to syphilis, and vice versa.

Yaws is readily communicable and man and monkeys may be successfully infected with material from one of the lesions of the skin [illegible]
disease and cause spread of [illegible]
of cells there is exudat[illegible]
as in miliary abscess. A [illegible]
buccal and conjunctival [illegible]

venereal and natural infection in man occurs most commonly through abrasions in the skin by direct contact with an infected case Flies especially *Hippealates* are generally recognized as potent factors in spread of the disease.

Symptoms in Initial stage—Poor native children, without clothing and with frequent skin wounds are the individuals most commonly affected During the incubation period which averages 3 to 4 weeks digestive troubles nocturnal headache *joint pains and an* irregular fever may be noted. These usually abate with the appearance of the initial papule (mother yaws) at the site of inoculation This les on which is almost always *extra gen tal* may be single or several papules may be grouped together and the regional lymphatic glands are enlarged and tender It is not painful but bleeds easily

The Secondary or generalised stage—From six weeks to 3 months after appearance of the initial lesion which may have dried up or which may still persist there occur again headache jo nt pains and fever and the secondary generalized eruption appears This eruption is made up of papules similar to [illegible]
frequent on the muco cutaneous junctions
or soles of foot The general zed stage
yaws tubercles come out in successive crop
is troublesome

Four groups of secondary skin lesions have been described —(i) Roseola which are fleeting and often go unnoticed They appear about twenty days after the primary sore (ii) Pianides appearing in interval between roseola and generalised eruptions (iii) Mucosal lesions on the lips and the tongue in plaques resembling those of syphilitic leucoplakia. (iv) Piamomas are vegetating papillomatous lesions oozing but not desquamate

Tertiary lesions of yaws are gummatous nodules and deep ulceration They may appear as destructive lesions of the naso pharyngeal region (tibia) dactylitis osteitis, periosteal nodes juxta articular nodes and gangosa (Rhinopharingitis mutilans) These may set in years after an attack of yaws

Differentiation Between Yaws and Syphilis

Das Gupta has summarised the following main points in which yaws differs from syphilis (i) Primary sores are practically always extragenital in position, (ii) secondary lesions never or only very rarely affect mucous membranes, (iii) alopecia and eye symptoms are absent (iv) in the tertiary stage vessels organs and nervous system are not affected, (v) the disease is not transmitted congenitally and *transmission* is affected by direct contact, (vi) infection with syphilis does not protect against infection with yaws, (vii) yaws is more easily transmissible to experimental animals than syphilis, and (viii) mercury does not appear to have any effect on yaws

Gangosa—The mucous membrane becomes honeycom bed with deep ulcers underneath The ulcerating processes progress rapidly becomes secondarily infected and destroy bones and soft parts eventually the whole of the nose and septum disappear The larynx is not affected Gangosa occurs in Fiji West Africa, and Congo in places where treatment is not available

Goundou occurs where yaws is common and follows closely the secondary stage There is persistent headache and thin nasal discharge accompanied by enlargement of the nasal processes of upper maxilla downwards and outwards till a projecting tumour as large as a fist forms As the exostoses grow the nasal passages are obstructed and vision is interfered w th Goundou is usually bilateral Treatment consists in surgical removal

Juxta articular nodes—The nodes are composed of irregularly distributed bands of connective tissues without elastic fibres and with poor blood supply Some observers do not connect it with yaws nor syphilis The tumours vary in size up to a golf ball and are very hard the skin over them is moveable at first but later becomes fixed, they are not painful and never suppurate. They are located in the external surfaces of extremities *and near the joints* They may become [illegible] and behave as neoplasms They may be mistaken for tumours produced by [illegible] *volvulus*

Treatment consists of [illegible] of [illegible] are troublesome

Diagnosis—Staining of the juice expressed from yaws tubercles by the Indian ink method, with Giemsa stain or under dark ground illumination is the best diagnostic procedure. The Kahn and Wassermann reactions are positive

Prophylaxis and Treatment—prophylaxis measures depend on the adoption of measures to prevent infection by direct contact with yaws cases which should be isolated and given prompt treatment with arsphenamine

In endemic areas fly protection measures should be generally adopted and abrasions should be protected by suitable dressing Clothing contaminated with the discharges of yaws is well known as a disseminating factor and should be boiled or disinfected

Arsenicals

The effect of arsphenamine in the treatment of yaws provides a most remarkable example of the specific action of a drug in therapy, and in early cases one single dose frequently effects a complete cure thus almost approaching Ehrlich s dream of a therapia magna sterilans In the treatment of early yaws

are absorbed

In the treatment of tertiary yaws more prolonged treatment is necessary and the following course is generally recommended During the first four weeks four weekly injections of neo-arphenamine or mapharside in the above mentioned dosage are given and bismuth subsalicylate injections 0.2 gm are given on the same days This is followed by another four weekly injections of arsenical alone and the course is terminated with another 8 weekly injections of bismuth subsalicylate

In the writers experience yaws occuring in India is a comparatively mild disease and most cases respond readily to one to three injections of a suitable arsenical or bismuth preparation Doses of 0 19 gm of neosalvarsan per kilo produced clinical cure in two injections in 93 3 per cent of cases in Fiji In other places more injections were required

Many bismuth preparations are equal in efficiency to neo-arsphenamine according to most authorities Sodium potassium bismuth tartrate bistoval bismuth arsenicals bismuth salicylate and metallic bismuth in oil are used. Other drugs used are stovarsol carbarsone and halarsol (oxyameno-phenyl dichlorarsine)

The use of 100 000 units of penicillin in 4 doses in nine to twelve hours is as effective as many incomplete courses of arsenicals given over a longer period It will cause the healing of secondary lesions and thus render the patient non infectious at least for the time being The skin and bone lesions respond more slowly but these cases had not healed previously despite prolonged and repeated arsenical and bismuth treatment Treatment with 15 000 units intramuscularly *every four hours* for seven days are stated to have produced a cure the lesions clearing up by the end of a week clinical cure being complete Serological reactions however remained unchanged Penicillin is likely to be effective in the treatment of pinta which is now known to be due to *T carateum or T herrejoni* (closely related to *T pallidum*)

3. The Relapsing Fevers

Two different types of Relapsing fever are recognised, and though caused by closely related spirochaetes they differ from each other in many important aspects such as epidemiology mode of transmission, severity of clinical manifesta tions and mortality rates

(1) Louse Relapsing Fever

The louse borne or Epidemic Relapsing fever is caused by *the Borrelia recurrentis* and allied varieties (*B carteri* of Indian relapsing fever, and *B berberi* of North Africa)

The disease is widespread throughout the world and particularly in India where the disease occurs in epidemic form throughout the country except in Bengal Assam and Orissa The infection is conveyed directly from man to man by the human louse *Pediculus humanus* either through a bite wound or a scratch wound being contaminated by infective material from a crushed louse.

B recurrentis is a spiral organism varying from 9 to 10 μ in length and 0 3 to 0 4 μ in breadth, and is found in the blood during the paroxysms of fever *Sometimes two or more spirochaetes are found attached end to end* The organisms are most plentiful after the first 2 days and may be easily stained by any of the modifications of the Romanowsky stain, such as Giemsas or Lieshmans

One attack confers immunity for a period of one to two years

The skin may show jaundice and peticheal hæmorrhages The internal organs are congested and hæmorrhagic. The liver and spleen are enlarged and may show areas of necrosis and infarcts Fatty degeneration of the liver is often a prominent feature The brain is congested and hæmorrhagic, the heart may show cloudy swelling and the bone marrow is hyperæmic Spirochaetes are plentiful in all the organs especially in the reticulo endothelial cells

In Northern India the incidence rises in autumn reaching its maximum in March or April after which there is a rapid decline

The disease generally comes on very suddenly with chill, severe headache dizziness and great prostration Severe pains in the back, arms and legs are prominent features The temperature rapidly rises to 104 or 105°F or higher, the pulse is rapid and the patient may be delerious Jaundice may appear if the fever has *lasted long* and an erythematous *eruption is sometimes seen over the* trunk and limbs

The fever generally lasts from three to six days after which it falls by crisis and is accompanied by profuse sweating This is followed by an afebrile period lasting from 3 to 10 days and then there is another attack of fever similar to the initial attack which again terminates by crisis There are usually four or five such relapses the febrile periods tending to become shorter, and the remissions longer Pneumonia diarrhoea dysentry transient paralyses or heart failure may occur as serious complications

Meningitic forms of louse borne relapsing fever have been described in North Africa which respond easily to treatment with arsenicals

According to Rogers and Megaw, the *mortality in India varies from 1 to* 50 per cent in different epidemics, the average being about 10 to 15 per cent If proper treatment with one of the arsphenamines is given promptly, the outlook is very good and the mortality is practically nil

The patient should be kept strictly in bed throughout the disease and for many days after The bowels are kept open, plenty of fluids are advised and a liquid but nutritious diet prescribed

Treatment

One injection of neoarsphenamine mapharside or one of allied compounds will terminate most attacks but relapses are common unless 2 to 4 injections are given The drug should never be given just before the crisis is expected as there is a very real danger of fatal collapse, due presumably to liberation of large amount of toxic material from the large number of spirochaetes destroyed Nor should arsenical drugs be given if cardiac, renal or hepatic disease is present The best time to administer the drug is soon after the beginning of a spell of fever or at the height of a paroxysm The dosage generally employed is neoarsphenamine 0 3 to 0 9 gm for adults and mapharside 0 04 to 0 06 gm Stovarsol by mouth has also been reported to be very effective in doses of 4 grs (0.25 gm) 5 or 6 times a day

Bismuth compounds have been used in resistant cases with good results

(2) Tick Relapsing Fever

Tick borne relapsing fever, is a non epidemic disease which is epizootic in certain rodents such as rats mice, etc, and is only incidentally transmitted to man by the [illegible]

[illegible]

O *lahorensis* in Iran and Northwest Asia, O *taloje* in South and Central America

The disease is predominantly a "locality" disease, and the infection persists in the ticks of certain houses and camping places The progeny of infected ticks are also infective. Ticks are very difficult to destroy as they usually live in cracks of walls ceilings and floor

Symptomatol

Tick brone relapsing fever is generally a less severe disease than its louse-borne prototype and the mortality is usually below 5 per cent The spells of fever are shorter in duration but more intense and usually last 2 to 4 days There are usually more relapses commonly 5 to 6 but the whole disease runs a shorter course Spirochaetes are not so numerous in the blood and certain complications such as diarrhoea and dysentery paralyses and iritis are more commonly encountered

Tre t ent

Treatment is on the same lines as for louseborne relapsing fever but generally speaking larger doses of arsenicals are required to overcome the infection.

Penicillin has been tried in the treatment of relapsing fever in doses ranging from 100 000 units in 24 hours to 900 000 units in 72 hours in a series of 11 patients 5 relapsed, in another series of 18 patients in which the treatment was combined with a single maximum dose of NAB there were 7 relapses The results indicate that neither penicillin nor NAB either alone or in combinat on is effective in preventing relapses of African tick fever

In cases of louse-borne relapsing fever, however in a series of 27 patients treated with total dose of 480 000 units for adults and 360 000 units for children the spirochætes disappeared within 24 hours and none were ever found again after 48 hours. All patients showed a rapid clinical recovery and there were no relapses The results with neoarsphenamine were also equally satisfactory

Tick borne relapsing fever has been reported in India but its being tick borne has only been a surmise, except in Kashmir where *O crossi* has been shown to be the carrier of infection *O moubata*—so far as is known has not been proved of relapsing fever in India.

In Kashmir the disease is mild the mortality is nil complications such as diarrhœa dysentery paralysis and iritis are unknown In untreated cases there are generally 5 to 8 relapses Penicillin has no effect in any dosage Ninety per cent of cases are cured by 1 0 gm of NAB the rest require a third injection of 0 6 gm

In Kashmir the vector and the disease are universally spread and not delimited to any particular endemic focus The incidence is high in summer (because the ticks are more active) but cases occur throughout the year

DDT and gammexane as dust on the floor and oily solution in the case of DDT and watery suspension in case of gammexane have proved effective in the control of these ticks

4. Rat-bite Fever

Rat bite fever is a relapsing fever occurring in people bitten by rats infected with *Spirillum minus (Spirillum morsus muris)* The disease is as widespread as the rodent host in its distribution and cases have been reported from practically all parts of the world It is however, much more prevalent in Japan than in other countries The organism is variable in size the usual being 2 to 6 μ long with a delicate flagellum with two to six curves but much longer forms up to 20 μ are occasionally seen, especially in cultures They are found at first in the blood of infected mice rats or guinea pigs and then become disseminated in the tissues particularly around the lips, tongue and nose They have not been found in the saliva and transfer of infection to man would appear to be through some break in the mucous membrane around the mouth

Another form of rat bite fever, which is quite common is that caused by *Streptobacillus moniliformis,* and is transmitted to man not only by the bites of rat, but also by cat bites

gy Four clinical types have been differentiated —(1) With general symptoms predominating (2) With local symptoms predominating (3) A type with severe pains (4) A type with neurological manifestations even paralysis

The incubation period varies from 5 to 40 days the average being less than 10 days Following this period during which time the wound of the rat bite heals there is usually a sudden onset with headache nausea and marked weakness the pulse is rapid and weak The scar of the wound becomes inflamed and even necrosis may occur The regional lymphatic glands are swollen and tender and there may be œdema of the hands and legs Fever rises rapidly to 101 to 102°F and within 2 or 3 days may reach 104°F or more and then remains high for another 2 to 3 days After this it falls rapidly to normal accompanied by profuse sweating The temperature remains normal for a few days during which time the local swelling and inflammation subside Joint pains sensory disturbances and symptoms of nephritis may be noted After a few days of normal temperature the fever again comes on later to disappear and re appear The successive paroxysms are usually *of less severity and separated by increasing intervals* A syphilis like eruption may occur but Wasserman reaction is usually negative

The primary wound may become infected with cocci bacilli and streptothrix and give rise to fatal septicaemia There may be as many as 12 of these febrile waves and the course of the disease may extend over several months There is an eosinophilia and during the febrile phases a leucocytosis of 12 to 15 000 is present

In infections caused by the *Streptobacillus moniliformis* the initial rat bite wound heals rapidly but marked constitutional symptoms appear 2 or 3 days after the bite Special features are severe arthritis and painful nodules in the muscles

Diagnosis—From history of rat bite The blood should be examined for spirilla by dark ground illumination during the early febrile periods Should this prove negative guinea pigs white mice or white rats may be inoculated with blood or gland juice care being taken that the animal is not already infected Spirillum infection is common among guinea pigs in India The Wassermann reaction is usually negative though in a few cases

Prognosis

One attack generally confers a lasting immunity in both man and animals Bacteriolytic antibodies have been demonstrated In Japan there was mortality rate of 10 per cent but since the advent of arsenical therapy deaths are rare Rat bite fever has been used in the treatment of general paralysis

Prophylaxis

Effective prophylaxis depends on rat destruction and prevention of contact with rats especially in darkened areas where bites are more likely to occur

Treatment.

Treatment—One or two injections of neoarsphenamine or some of its derivatives will usually cure the disease and the ordinary doses of 0 3 to 0 6 gm are usually sufficient The injections should be given early in each spell of fever and not at the end of the paroxysm in the same way as in relapsing fevers Since recurrences are common (especially in Japan) when less than 3 injections are given, a course of 3 to 6 injections is advisable Otherwise treatment is symptomatic Aspirin relieves severe joint pains Strychnine may be given for weak heart Local treatment of the wound or even excision are of little value though it is advisable to cauterize the wound with phenol or tincture iodine.

Antimony preparations, such as stibosan have been successfully used by some workers

While infections with *S minus* respond well to arsenotherapy, those with *Streptobacillus moniliformis* are quite resistant and as a consequence penicillin was tried successfully (1944) Penicillin in doses of 10 000 to 15 000 units administered intramuscularly every 3 hours, continued for 7 days is curative Blood cultures were found to be negative and arthritic symptoms were improved and later disappeared The patient has no relapse for a year

The growth of streptobacillus from the patients blood was inhibited by 0 001 unit of penicillin per ccm in media in which it normally showed a luxuriant growth

5. Other Spirochaetal Diseases

(1) Infectious Jaundice (Weil's Disease)

Aetiology

Infectious [illegible]
onset with high [illegible]
about the 3rd [illegible]
especially epist [illegible]
enlarged The disease is produced by *L. icterohaemorrhagica and L canicola*

The disease is of world wide distribution and is common in Japan and Egypt and is also endemic along the Mediterranean coast In recent years cases have been reported from many countries of Europe and America. The disease is also reported to be frequent in Burma and the East Indies. Although the disease has been presumed to exist in India for a long time the first case was reported by Chopra and Das Gupta in 1937 Since then a number of cases have been reported. Ordinarily only sporadic cases occur but localised outbreaks are seen. In cold countries it is common in the warmer months

Mode of transmission

Human infection results from ingestion of food or water contaminated with the urine of infected rats, the leptospira gaining entrance through the skin and mucous membranes, the conjunctivae mouth and intestines Bites by infected rats may convey the disease Bathing in infected water is a common mode of spread Mice rabbits and other rodents may be infected Infections occur from handling soil and sewage and infected laboratory rats attendants should wear rubber gloves when handling these animals.

Leptospira icterohaemorrhagica

The *Leptospira icterohaemorrhagiae* was first discovered in 1915. It is a slender organism varying in size from 6 to 14 μ by 0.25 μ The spirals are closely placed together giving the appearance of a series of small dots. It is actively motile and may be demonstrated by the dark ground illumination, and by Giemsa's stain or by the silver impregnation method or in Indian ink preparations. The organism is frequently found in the blood during the first 3 or 4 days of the disease. It is found in the liver and kidneys of inoculated animals, and can be grown on special media containing blood serum.

After an incubation period of *from 6 to 12 days the* disease sets in abruptly with fever rigors headache muscular pains and vomiting wh ch may last for a few days and then pass off Often it lasts for two to four weeks The fever is of irregular type and runs between 102 to 104°F for the first 3 or 4 days wl en it begins to fall by lysis occasionally by cris s about the fifth day In severe cases the temperature may not decline until about the 10th day *After a few days* of apyrexia or moderate temperature there is a tendency for a second rise towards the end of the [illegible] when a slow convalescence sets in In [illegible] *second or third* day with marke [illegible] and sometimes slight enlargement of [illegible] high coloured and contains albumin [illegible] pig ent. Early in the 2nd weeks bile stained urine of low specific gravity is usually secreted in large amounts. Sleeplessness and nocturnal delerium occur and in unfavourable cases the cond tion may resemble the typhoid state Pains in the nape of the neck and calf muscles are common In some outbreaks haemorrhages particularly expistaxes and malaena are common hæmaturia is rare Petech al rash is common in some outbreaks and a measly or urticarial eruption may appear on fifth to twelfth day

There is leucocytosis from 10 000 to 20 000 red cells and haemoglobin are both decreased and anæmia may last for weeks Pulse is rapid at first but with the onset of jaundice is slowed blood pressure is low Occas onally irido-cyclitis may occur

The Vandenberg reaction is directly positive, the blood urea may be raised 50 to 397 mgm and death from uraemia may occur Leptospirae which are found in the blood dur g the early days soon disappear and after 7 to 19 days may appear in the urine where they may persist for as long as 6 weeks.

The mortality figures vary in d fferent countries from 4 to 32 per cent in Europe to 48 per cent in Japan In India the mortality is high like Japan

Diagnosis—Accurate diagnosis is only possible in the laboratory and depends on (1) d scovery of leptospirae in fresh blood (2) by culture from blood (3) by inoculation of blood or ur ne into guinea pigs intraperitoneally and making smears from liver and spleen at the height of fever (4) detect on of organism in urine (5) serological examina t on The disease must be distinguished from bilious remittent fever syph l s of the liver yellow fever liver abscess relapsing fever and black water fever

Prophylactic measures include extermination of rats, prevention of contamina tion of food and water by discharges from rats avoidance of bathing in infected pools canals and sluggish rivers Sewer workers should be given protective inoculation Laboratory workers handling rats and mice should wear rubber g oves Prophylactic vaccination with killed cultures of the organism or a phenolized emulsion of the liver containing the leptospirae have been tried with favourable results More recently living avirulent cultures have been used for this purpose but these are not without danger

Treatment—The treatment is largely symptomatic on the same lines as yellow fever The patient should be given a liquid diet and the bowels should be kept open regularly Mild cases require little treatment but in severe cases there may be severe toxaemia vomiting and nephritic symptoms which require energetic treatment Intravenous injections of 500 to 1 000 ccm of a glucose solu tion should be given A polyvalent antiserum is of value in severe cases and injections of 20 ccm should be given intravenously two or three times a day, for at least three to four days The serum is most beneficial if given early in the disease and its value is greatly reduced if it is given after the jaundice has appeared Convalescent serum given in doses of 30 cc for three or more days has been reported to have given good results

If vomiting is severe nutriment may be given in the form of rectal enemas or substantial quantities of glucose may be given parenterally Calcium injection are claimed to be of some value

It has recently been demonstrated experimentally that *L. icterohaemorrhagica* infections are sensitive to penicillin therapy, which should be continued for from 7 to 10 days; and total of 1,000,000 units being given.

(2) Japanese Seven Days Fever, (Nanukayami)

This disease is quite different from the Indian seven days fever which is a form of [illegible]

is leucocytosis.

The spirochaetes occur in the blood in small numbers and are difficult to detect except by expert laboratory investigation as in Weils' disease

Short spirochaetal fever occurs in Dutch East Indies lasting for 2 to 7 days Several distinct strains of leptospira have been isolated Rats and less commonly cats are the reservoirs of infection.

Megaw has pointed out that a number of these leptospira fevers occur in different parts of the world which have certain features in common. They are usually of short duration and have a tendency to relapse, they all produce jaundice, albuminuria and leucocytosis They are liable to be confused with the dengue group A severe type of non spirochætal febrile jaundice, probably due to a virus occurs which is difficult to differentiate from Weils' disease The troublesome cases of jaundice occuring after inoculation against yellow fever combined with immune serum were suspected to be due to this virus originating in the blood used in preparing the vaccine. It is very difficult to sterilize any serum against viruses by filtration

Vincent's angina is generally regarded as being due to a spirochæte and the *Bacillus fusiformis* Injections of arsphenamine are very useful in this condition The influence of arsenicals on the saprophytic spirochætes of the mouth is very doubtful and the role of spirochætes in the production of bronchitis is highly uncertain In cases of pulmonary gangrene associated with spirochætes in the lungs, excellent results have been obtained by injection of arsphenamine.

6. Arsenical Compounds

Although arsenic was first used in medicine in England in the early part of the 17th century, its authentic history does not begin till Sir Thomas Fowler introduced Fowler s solution in 1786 Its employment in the treatment of protozoal disease was first suggested by the famous explorer, Dr Livingston who recommended its use in the disease caused by the tsetse fly in animals.

(1) Pharmacological Action

Arsenic is toxic to all animals which possess a central nervous system and to most of the higher plants, but not to all lower organisms. Its antiseptic action is feeble and it is not classified as a protoplasmic poison. Arsenious acid is only one-tenth as strong an antiseptic as perchloride of mercury Compounds of arsenic have no effect on the activities of such ferments as pepsin Some of the pathogenic protozoa, *e g*, trypanosomes, show a most extraordinary susceptibility to arsenic and are destroyed in 1 in 200,000 dilution in the blood, while free living protozoa may survive in 1 in 5 000 solution

Local action

Arsenicals do not coagulate proteins nor change them in any way and, therefore they produce very little irritation of raw surfaces and mucous membranes, but the cells die slowly after prolonged contact with them They are for this reason used for destruction of exposed dental nerves and epithelial growths of the skin When applied to mucous membranes and deruded surfaces they produce much pain and deep destruction of the tissues Arsenical dermatitis occurs among workers who handle it.

In man, arsenic has a beneficial effect on the nutrition of the skin, the subcutaneous fat is increased and the complexion is improved, it renders the coat of domestic animals such as the horse thicker and more glossy In veterinary medicine it is commonly used for this purpose and solutions of arsenic are used as 'dip' to rid animals of ticks, etc. Large

doses cause eruptions and keratosis, but this is not due to vaso-dilator effects nor is there evidence of any action on the nerves Arsenic compounds undoubtedly during their excretion have a marked action on the intestinal epithelium and it is probable that they also exert a specific action on the epithelial cells of the skin. The arsenicals also produce a brown colouration of the skin of the face and other parts which is known as 'melanosis

Small doses such as *one sixtieth to one fiftieth* of a grain of the oxide are said to

tion poured into the lumen of the gut causes distension increased peristalsis and profuse rice water stools collapse and death may follow

Circulation Very small doses have no effect on the isolated frog's heart large doses depress it The mammalian heart is little affected but large doses intravenously produce a fall of blood pressure due to paralysis and dilatation of the capillaries The vessels of the splanchnic area seem to be more susceptible to the action of arsenic than those of the rest of the body *Their dilatation leads to congestion of the bowels fall of blood pressure* and collapse It has been experimentally shown that the capillaries are injured and become more permeable after arsenic poisoning Intravenous injections of large quantities of saline cause œdema in animals to whom toxic doses of arsenic compounds have been given while no such effects are produced in normal animals

Blood The action on the blood is still obscure though it is largely prescribed in anæmia Arsenic probably produces increased vascularity and stimulates the bone marrow to increased formation of erythrocytes
doses however no chang
been observed In toxi
the bone marrow and an
protect the red cells from
action in diseases like pernicious anæmia

Respiration Small amounts have a distinct stimulating effect on the respiratory centre large amounts depress it *Small doses are said to depress the peripheral terminations of the vagi in the lungs, hence it is used in asthma*

us

Central nervous system In the frog a descending paralysis is produced the animal ... reflexes *the terminations of the motor* peripheral neuritis and characteristic and in severe cases the spinal cord

...bolism of ...ised

ody

Fate in the body
membranes Poisoni
preparations After

Normal occurrence of arsenic in the body Arsenic is a normal constituent of human tissues, but it plays no part in their functions In man it occurs especially in the thyroid gland (0 16 mgm) in the thymus brain skin and hair in the blood it has been estimated to be present to the extent of 0 3 mgm per 100 ccm of a dried specimen Arsenic to the extent of 0 3 mgm has been found in 100 gm of dried normal urine *It is found* ... for medicinal purposes and through the milk it passes from found in the lungs The arsenic such as milk, eggs fish vegetable ... of 1902 the quantity ...unt ...eds

Excretion Arsenic disappears rapidly from the blood when injected and is fixed in certain tissues It is chiefly found in the liver, kidneys walls of the stomach and intestines, in the spleen and lungs. Much smaller quantities are found in the muscle and nerve tissue With oral administration the main part leaves by the fæces, with hypodermic injection, by the urine After a single dose excretion of arsenic goes on for ten days and after repeated doses it may continue for months. It is found in tissues especially in the hair and epidermis for months after its disappearance in the urine and fæces.

Excretion.

Tolerance [illegible]

Tolerance

It is said to produce intoxicating effects stimulation of sexual and respiratory functions and a feeling of strength and well being Withdrawal does not cause any abstinence symptoms.

The phenomenon of tolerance to arsenic has not been satisfactorily explained. Some consider that the tolerance is limited to the intestinal epithelium, which no longer undergoes inflammation and necrosis under arsenic and absorbs less of this drug Considerable quantities of arsenic, however occur in the urine of arsenic eaters and therefore absorption must occur Another hypothesis is that an antitoxin is formed Tolerance is acquired by the pathogenic protozoa and arsenic fast strains of trypanosomes have been experimentally produced

(2) Arsenic Compounds

Inorganic Arsenic compounds All inorganic compounds of arsenic are very poisonous but metallic arsenic is insoluble in water and passes through the alimentary canal for the most part unchanged and without exerting much action. It is probable that the activity is due to a compound of oxygen and arsenic appearing as an ion The most important oxides are As_2O_3, or As_4O_6 called arsenious anhydride commonly known as 'white arsenic' and As_2O_5 arsenic anhydride

Arsenic and arsenious compounds

Arsenic and arsenious compounds In *arsenic* compounds arsenic is pentavalent, and in *arsenious* it is trivalent Trivalent arsenic (arsenites) is generally much more toxic for protozoa bacteria and yeast cells than is pentavalent arsenic (arsenates) The pharmacological action of arsenic is said to be due to the negative ion AsO_3 of arsenious acid H_3AsO_3, in which arsenic acts as a trivalent element. It is held that compounds in which arsenic is pentavalent, *i e*, derivatives of arsenic acid H_3AsO_4 are reduced to arsenious compounds in the tissues The ratio of toxicity of arsenious to arsenic acids when given intravenously to rabbits is 6 to 1 and for the excised frog's heart 300 to 1

Organic compounds of arsenic The organic compounds in which arsenic is combined with carbon behave somewhat differently from the inorganic compounds As long as they are present in an unchanged condition in the body they do not exhibit the ordinary action of arsenic During the process of oxidation and reduction in the body some arsenic is gradually split off and the action of arsenic is produced For this reason the action is delayed and is mild Both trivalent and pentavalent arsenic can be readily introduced into a large variety of organic molecules The decomposition of organic arsenicals is, as a rule slow and passes through many intermediate stages of simpler organic molecules a considerable portion is in all probability excreted from the body in organic form during this process The organic compounds are much more toxic to pathogenic protozoa infesting the animal body and that is the reason why they are largely used in the treatment of diseases produced by these parasites. When these compounds are tested *in vitro* they produce little or no toxic effect on the parasites and they therefore require the co-operation of the tissues of the host to become effective

The pulmonary pressure is enormously increased after intravenous injection of arsphenamine probably due to the obstruction of the pulmonary circulation caused by the alkalinity of the solution and possibly also to the presence of an embolic precipitate formed in the vessels The specific action of the drug on the musculature of the arterioles may be another factor concerned Injections of salvarsan and neo-salvarsan in patients lower the arterial blood pressure.

Absorption and fate of the organic arsenic compounds The rate of absorption varies with the modes of administration After intramuscular injection in rabbits of neoarsphenamine 80 per cent of the arsenic had been absorbed during the first week and 90 per cent by the end of the second, while only about 5 per cent remained in the tissues at the end of six weeks Arsphenamine or neoarsphenamine when given intravenously leaves the blood

Absorption and fate of the organic arsenic compounds

stream rapidly, at least three fourths disappearing in a few minutes Observations in animals show that after a single injection of one of the organic arsenicals the arsenic is found abundantly in the organs whose capillaries would mechanically absorb the flocculates, the liver spleen and the lungs, the size of the former making it the principal storehouse of arsenic The liver gets rid of arsenic by excreting it in the bile where its concentration is higher than *in the blood, of all the tissues the bones retain arsenic the longest* The brain, spinal cord the nerves and the cerebro-spinal fluid contain traces.

Excretion of organic arsenicals After a single dose of *pentavalent compounds the* arsenic is excreted promptly and mostly in the urine With continued administration, the excretion is prolonged, the greater part leaving within 3 days but traces continue for 3 weeks the effect is cumulative A small part is excreted by the fæces The excretion of atoxyl commences early about 85 per cent of the dose injected is excreted in the urine within 24 hours The reason for this rapid excretion is that pentavalent arsenic is not fixed in the body cells

Trivalent compounds Salvarsan is excreted very slowly the maximum amount of arsenic occurring in the urine being about 1·0 per cent in 24 hours and a somewhat larger amount occurs in the fæces the total amounting to about 3 per cent The drug is excreted more slowly after intramuscular than after intravenous injections About 80 per cent leaves the blood in five minutes after an intravenous injection but small quantities circulate in the blood unchanged for 12 hours and trace
days The greater portion of the drug is
which it is released slowly Neo salvarsan
than salvarsan and is said to be excreted

Classes of organic arsenic compounds The starting point of all these are two acids known as arsinic acid (trivalent) and arsonic acid (pentavalent)

(B) Aromatic (Benzol) series The development of this series of compounds is due to the efforts of Ehrlich to obtain drugs which would destroy the organisms producing disease in the body The starting point of Ehrlich's investigation was atoxyl which is the sodium salt of p am nophenyl arsonic acid known as arsanilic acid. By multiplicity of changes synthesis and experiments on thousands of infected animals he endeavoured to find which atoms or groups of atoms and what grouping in the molecule increased the affinity for the parasites and reduced the toxicity to the cells of the host most. Substitutions in the NH_2 group may cause profound differences in the effects of the compounds—sometimes an increase and sometimes a decrease in the therapeutic effect If acetamide
... ten times less toxic

The aromatic compounds of arsenic may be divided into —

(*a*) Those in which arsenic is pentavalent *Atoxyl* is the monosodium salt of p-aminophenyl arsonic acid or p arsanilic acid It is also known as *arsamin* or *soamin* *Arsacetin* or sodium acetyl p-aminophenyl arsonate is tolerated in much larger doses than atoxyl. *Carbarsone* or 4-carbamino phenyl arsonic acid was first prepared by Ehrlich in 1909, it has been recently used in the treatment of amœbic dysentery *Tryparsamide*

(sodium n phenyl glycinamide p arsonate) was discovered at the Rockefeller Institute New York. *Stovarsol* (sodium 3 acetylamino 4 oxyphenyl arsonate) *Acetylarsan* (a simple derivative of stovarsol) *Treparsol* (3 formylamino-4 hydroxyphenyl arsonic acid) are some of compounds used

(b) *Those in which arsenic is trivalent Arseno benzene derivatives* —These compounds have a di benzol or arsenobenzene nucleus coupled together by two trivalent atoms of arsenic *Salvarsan* is No 606 of Ehrlich s series (dihydrochloride of d oxy diamino-arseno-benzene) is also known as *arsphenamine*, *kharsivan arsenobenzol arsenobillon* etc.

Trivalent compounds

Neo salvarsan (No 914 of Ehrlich s series) is a condensation product of salvarsan It is known as *neokharsivan neoarsphenamine novarsenobenzol* and *novarsenobillon* *Silver sodium salvarsan* and *silver neo salvarsan* have a high chemotherapeutic index

Sulpharsenol or sulpharsphenamine is d sodium d hydroxy d amino-arsenobenzene n dimethylene sulphonate It is also known as *sulpharsenobenzene kharsulphan myosalvarsan.*

Oxophenarsine Hydrochloride (Mapharside) A more recent preparation (3 amino 4 hydroxyphenyl arsine oxide hydrochloride) is known as mapharside It was accepted by the U.S.A Council on Pharmacy and Chemistry for inclusion in New and Non-official remedies in 1943 and has more recently been included in the U S Pharmacopiaea

(3) Modes of Administration

Local application One in 1 000 solution of salvarsan and neo salvarsan exert spirochæticidal effects on *T pallidum* and *T pertenue* in chancres mucous patches and other syphilitic and frambœsial ulcers Under the microscope 1 in 1 000 solution destroys the motility of the spirochætes immediately

Oral and rectal administration Arsphenamine is absorbed when given by the mouth but produces symptoms of gastro intestinal irritation Its therapeutic effect is feeble Arsenical compounds are given by the mouth in treatment of amœbic dysentery and pentavalent compounds such as carbarsone stovarsol and treparsol are now sold in tablet form The rectal method has been tried with salvarsan but is even inferior to the oral route

Subcutaneous and intramuscular injection Subcutaneous and intramuscular injections have been tried in aqueous solution olive oil or liquid paraffin but salvarsan tends to deposit locally and gives rise to pain and swelling even when the solutions are carefully neutralised or mixed with olive oil before injection The rate of absorption from the muscles depends primarily on the degree of injury to the tissues neo-salvarsan which is neutral in reaction produces less irritation than salvarsan which is acid and is therefore absorbed 5 to 6 times more quickly

The absorption of sulpharsphenamine is considerably more rapid It is the only one of the trivalent arsenicals which can be safely given by this route and produces the therapeutic effects desired The advantages of the subcutaneous and intramuscular routes are that acute toxic reactions are much less common though they are not altogether eliminated the disadvantages are that local reactions are produced The pentavalent compounds such as atoxyl tryparsamide stovarsol as a group produce less local reactions than trivalent compounds

Intraspinal intraperitoneal and intrapleural methods Even when well diluted with spinal fluid the arsenical compounds given in the spinal canal produce considerable irritation of the cord causing severe shooting pains the respiratory and cardiac centres are not affected This form of medication is as a rule not employed As intraperitoneal and intrapleural injections produce irritation these are not recommended

Intravenous route The intravenous method is the one usually adopted. The disadvantage of ' - - ' ' rapidly eliminated and consequently the hort Besides the technique is more di eactions is higher due to factors inherent in the drug itself or in its solvents The main advantage is the freedom from pain and disability when intravenous injections are properly given The intravenous route is preferred in acute early stages of syphilis for rapid destruction of spirochætes in lymph blood and tissues in later stages however when most of the organisms are fixed in the tissues the intramuscular and subcutaneous routes are preferred by some because the absorption and excretion rates are reduced and spirochæticidal effects are enhanced Some give intravenous and intramuscular injections alternately After intravenous injections the reticulo endothelial cells of the *spleen liver and lymph glands become swollen* and granules of arsenic can actually be demonstrated in them After very large doses of neo salvarsan the granules can be demonstrated in the capillary endothelium the intestine and the salivary glands as well

The elaborate technique of prepartion, neutralisation and injection of salvarsan is no longer necessary with neo salvarsan and other allied compounds as they have a neutral reaction when dissolved in distilled water The temperature of the solution should not exceed 22°C or 71°F Slight febrile reaction generally occur after the first injection if *this reaction reappears in the course of the treatment* (*i e* on subsequent injections) it is a sign of intolerance. The rate of injection of these compounds is of importance A concentrated solution injected slowly is as well borne as a dilute solution injected rapidly, but if injected rapidly they both produce a higher incidence of toxic reactions With solutions of neo

pass may produce toxic symptoms due to the inferior quality of rubber

A study of the various vehicles for the injection of the novarsenobenzol compounds has been made In order to get the quickest and best results in the treatment of syphilis the tendency is to give these preparations in doses as large as possible and to shorten the interval between courses This unfortunately often produces toxic and sometimes fatal results In order to avoid angioneurotic symptoms dermatitis and other complications a number of diluents other than saline were tried Blood serum glucose saccharose calcium chloride egg albumin and gum have all been tested Of all these glucose appears to be the best as to some extent it prevents oxidation Thirty ccm of a 30 per cent solution of glucose given intravenously in conjunction with neo arsphenamine is said to increase the efficacy of the latter

(4) Organic Compounds of Arsenic

(i) Atoxyl

Synonyms —Soamin Sodium p arsanilate, Arsamin Trypoxyl Atoxylon

It is a white odourless crystalline powder with a saline taste soluble in 6 parts of water and 125 parts of alcohol It contains 27 2 per cent of arsenic. Under the misleading name of atoxyl (for the substance is quite toxic) it was extensively used at one time in trypanosomiasis (sleeping sickness) syphilis and other protozoal diseases A number of compounds similar to atoxyl have been tried in trypanosomiasis *Soamin* is practically identical with

sterilised before use

Atoxyl has no action on the trypanosomes *in vitro* and can only become effective when

Therapeutic uses Atoxyl was introduced in the treatment of trypanosomiasis many years ago and is still used in animals. It acts on the parasites in the blood, but has less effect on those which have infected the lymph glands On administration of this drug the parasites disappear from the blood but the supply is being constantly renewed from foci in the lymphatic glands and in the nervous system

Toxic effects Toxic effects produced with doses exceeding 0.5 gm resemble the acute

Toxic effects

also injured. Ophthalmoscopic examination shows at first no changes save that the retinal arteries may be narrowed and the veins somewhat hyperæmic later there is complete optic atrophy The most important factor in the production of optic lesions is the presence of the amino group in the para position to the arsenic

(ii) Tryparsamide

Synonyms —Moranyl Sodium n phenyl glycinamide p-arsonate

This compound was synthesized and developed in the Rockefeller Institute It is a white odourless crystalline powder containing not less than 25 1 and not more than 25.5 per cent of arsenic. It is very soluble in water forming a neutral solution which is comparatively stable so that a 10 per cent solution can be boiled without decomposition Its toxicity is very low and it is only slightly irritant and can be given intramuscularly, intraperitoneally (in animals) and intravenously

er doses nervous There are tremors, inco-ordination of movements, clonic spasms weakness and prostration the appetite is lost and animals are emaciated and occasionally suffer from diarrhœa The pathological changes consist of vascular dilatation congestion, scattered ... ative changes in internal organs Th... cted with *T brucei* was found to be ... and intravenously and 0.275 gm wh...

peutic ... for mice w... Its trypanocidal activity 100 solution In mice in the ratio between curativ of atoxyl

Dosage and method of administration In adults the dose is 2 to 3 gm and in children 0 5 to 1 gm according to age The drug has been tried in sleeping sickness in doses of 2 gm intravenously (0 112 gm per kilo body weight) Solutions should be freshly prepared 2 to 3 gm being dissolved in 10 ccm of cold sterile water Such solutions should be clear but it is advisable to filter them through sterile filter papers any turbidity necessitating the rejection of the solution Boiling should be avoided as it may produce decomposition and toxic compounds The drug is well tolerated intramuscularly in 20 per cent solution 30 per cent solutions produce more discomfort and may lead to abscess formation It may be given by this route but usually the intravenous route is preferred Subcutaneous injections are not recommended as they produce irritation and suppuration Ten weekly injections of 40 mgm per kilo body weight in a 10 per cent solution are considered safe The toxic effects of this drug are confined to doses close to the MLD and the recovery of animals from sublethal intoxications is remarkably rapid and complete This makes possible the repeated administration of very large doses of the drug at comparatively short intervals without incurring the danger of cumulative toxic action A high degree of tolerance develops

Toxic effects Untoward effects are not common The most serious such as amblyopia nitritoid reactions and exfoliative dermatitis have not been noticed and jaundice is a rare complication As a rule 80 to 90 per cent of the drug is excreted during the first 24 hours after injection but in certain individuals it is excreted slowly and they are more susceptible to the cumulative effects of the drug

The untoward effects generally appear after the fifth or sixth injection the symptoms consisting of a sensation of dazzling on examination the fundus is found to be hyperæmic the visual fields are contracted on the nasal side In severe cases contraction goes on till complete blindness results Involvement of the optic nerve is by no means rare in neurosyphilis All such cases should therefore be thoroughly examined by an ophthalmologist before treatment with tryparsamide The visual fields including the fields for colour vision should be mapped out before its use and should be checked several times during the course of treatment Occasionally vomiting slowing of the pulse and loss of consciousness may occur immediately after an injection similar to those seen with arsenobenzene Remote effects are shedding of the nails albuminuria and dermatitis Visual disturbances are seen with larger doses If these occur a suitable interval between injections prevents them Doses of 3 0 gm and over *should not be given oftener than once a week* If amblyopia develops during the treatment of trypanosomiasis tartar emetic is substituted for 3 weeks Sodium thiosulphate injections appear to be ineffective in preventing amblyopia

Therapeutic uses Syphilis Experiments on rabbits showed that this drug possesses the power of tissue *penetrability to a marked degree, extensive cutaneous* and subcutaneous lesions in these animals retrogressed and healed very quickly under its effect Tryparsamide is not effective against primary and secondary syphilis nor against the gummata or earlier cerebro spinal manifestations It appears to possess the power of penetrating into the tissues especially nervous tissues to a much greater extent than some of the other arsenicals It has been tried in neuro syphilis with good results

The best results have been obtained in patients with early symptoms of dementia paralytica and nearly 50 per cent of cases are said to have shown varying degrees of symptomatic improvement In tabetics the drug is less satisfactory as also in advanced cases of dementia in fact in some of these

cases it may hasten the progress of disease It is not advisable to use this drug in any other form of syphilis except that of the nervous system and it is often used as a follow up treatment after malaria therapy

Tryparsamide is the drug of choice in later stages of human trypanosomiasis, in combination with Bayer 205 quite a large number of cases are cured (see trypanosomiasis) Tryparsamide is sold either as powder in 50 gm bottles or in ampoules containing 1 2 and 3 gm

(iii) Stovarsol (Acetarsone)

Synonyms —Ehrlich 594 Fourneau 190 Acetarsone Stovarsolan Acetylamino-oxyphenylarsonic acid Orsanine... It contains 27 1 to 27 4 per cent of arsenic It is absorbed rapidly has a low toxicity and is excreted rapidly in the urine Saulet (1927) found that stovarsol was lethal to *E histolytica* culture within 24 hours in dilutions of 1 in 600. He noted that it was more active in the presence of liver extracts

Syphilis It was first introduced into medical practice in 1921 22 in the treatment of malaria and amoebic dysentery as a prophylactic against syphilis, and for the treatment of spirochetal infections Administration by the mouth produced healing of primary lesions in rabbits and monkeys.

In amoebic dysentery the drug has been tried in those cases which had resisted emetine treatment in doses of 0·5 gm in pill form twice daily for a period of 10 days. Occurrence of a measles like rash was not uncommonly met with and cases of acute exfoliative dermatitis have been recorded after administration of stovarsol Knowles treated 32 patients mostly chronic in Calcutta the ratio of probable cures to failures in these was 1 : 1 The drug has also been tried in the treatment of malaria and relapsing fevers

Toxic symptoms Cases of poisoning with stovarsol following its administration in dysentery in 2 gm doses daily have been recorded Fever was the first symptom followed 2 days later by diffuse erythema, dryness pruritus and urticaria Rashes appeared all over the body and on the legs and face in severe cases it may pass on to exfoliative dermatitis Oedema jaundice colic diarrhoea, albuminuria, coryza, bronchitis urticaria, ocular troubles, giddiness, collapse and glycosuria may occur Acute nephritis with casts in the urine may occur after injection The drug should not be given for more than 10 days at a time the second course should be given after a suitable interval

Toxic sym

(iv) Treparsol and Acetylarsan

Synonyms Fourneau 257 Sodium formylamino 4 oxyphenyl arsonate *Formyphenarsine*

It is said to be suitable for administration by the mouth in 1·0 gm doses In the intestines treparsol is split up into formic acid and meta amino-para-oxyphenyl arsenic acid which is the active principle of stovarsol and is said to act directly on intestinal parasites specially protozoa Although courses extending over 4 weeks have been recommended it is not advisable to give it for more than 10 days at a time Slight diarrhoea may occur and fatal cases have been recorded after prolonged use Treparsol is excreted mostly in the urine

Acetylarsan (hydroxy acetyl amino phenylarsinate of diethyl amine) can be given by intramuscular and subcutaneous injections but headache vomiting and diarrhoea are frequently produced erythema albuminuria, and jaundice may occur

(v) Arsphenamine

Synonyms Salvarsan Kharsivan, Diaminodioxyarsenobenzene Arsenobenzol Arsenbillon, Dioxy diamino arsenobenzol dihydrochloride Ehrlich Hata 606 Arsphenamine Amino-arsenophenol,

Salvarsan was first prepared by Bertheim and tested by Ehrlich and Hata in 1910 The dose for women is 0·3 to 0·4 gm and for men 0·4 gm in 250 ccm of solution medium It is a yellow crystalline powder containing 31·5 per cent of arsenic It is readily oxidized by the air and so is kept in vacuum tubes Salvarsan though it does not kill these organisms in vitro has a very pronounced effect on these organisms in vivo It is

Dosage and method of administration In adults the dose is 2 to 3 gm and in children 0 5 to 1 gm according to age The drug has been tried in sleeping sickness in doses of 2 gm intravenously (0 112 gm per kilo body weight) Solutions should be freshly prepared 2 to 3 gm being dissolved in 10 ccm of cold sterile water Such solutions should be clear but it is advisable to filter them through sterile filter papers any turbidity necessitating the rejection of the solution Boiling should be avoided as it may produce decomposition and toxic

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Toxic effects Untoward effects are not common The most serious such as amblyopia nitritoid reactions and exfoliative dermatitis have not been noticed and jaundice is a rare complication As a rule 80 to 90 per cent of the drug is excreted during the first 24 hours after injection but in certain individuals it is excreted slowly and they are more susceptible to the cumulative effects of the drug

The untoward effects generally appear after the fifth or sixth injection the symptoms consisting of a sensation of dazzling on examination the fundus is found to be hyperæmic, the visual fields are contracted on the nasal side In severe cases contraction goes on till complete blindness results Involvement of the optic nerve is by no means rare in neurosyphilis All such cases should therefore be thoroughly examined by an ophthalmologist before treatment with tryparsamide The visual fields including the fields for colour vision should be during the course loss of conscious those seen with arsenobenzene Remote effects are shedding of the nails albuminuria and dermatitis Visual disturbances are seen with larger doses If these occur a suitable interval between injections prevents them Doses of 3 0 gm and over should not be given oftener than once a week If amblyopia develops during the treatment of trypanosomiasis tartar emetic is substituted for 3 weeks Sodium thiosulphate injections appear to be ineffective in preventing amblyopia

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The best results have been obtained in patients with early symptoms of dementia paralytica and nearly 50 per cent of cases are said to have shown varying degrees of symptomatic improvement In tabetics the drug is less satisfactory as also in advanced cases of dementia in fact in some of these

The drug can be given by the intravenous or intramuscular route, the former being preferable It should never be given subcutaneously For gravity intravenous injections 12.5 ccm of freshly double distilled pyrogen free water should be used for every 0 1 gm of the drug The solution should be warmed to not more than 20 to 22° (68 to 71 68°) before injection For intramuscular injections 0 15 gm is dissolved in 0 3 ccm of freshly distilled water, this will give an isotonic solution Concentrated solutions 0 1 gm in 0 5 ccm of freshly distilled water may be given by a syringe It is advisable to draw up equal amounts of blood in the syringe containing the solution and then reinject very slowly, the [illegible]

should be preferably kept in a cool dark room or in a refrigerator and should be not more than six months old Neosalvarsan is sold in ampules containing 0 15, 0 3 0 6 0 75, 0 9 gm

(vii) Oxophenarsine Hydrochloride (Mapharside)

Synonyms —Mapharside (Parke Davis & Co) Phenarsine Hydrochloride (Winthrop) Clorarsen (Squibb)

Mapharside is a tri valent arsenical and contains 31 per cent arsenic. It is now officially designated in the U S P as oxophenarsine hydrochloride This preparation was introduced by Parke, Davis and Co in 1932 and has been in [illegible]

water to form a solution suitable for intravenous injection

In 1941, the therapeutic possibilities of buffered solution of oxophenarsine hydrochloride was presented in a report by the U S Council on Pharmacy and Chemistry based on a series of animal experiments and on a clinical study of 171 patients treated over a period of 2 years It was concluded that the drug buffered with sodium citrate is a safe and effective drug in the treatment of [illegible] on of darkfield negativity of early lesions [illegible] effectiveness in producing sero-negativity [illegible] relapses (5) low incidence of abnormal spinal fluids in early syphilis (6) absence of severe immediate reactions to its administration and relatively low number of reactions in general

It is claimed for mapharside that it is the active derivative of arsphenamine formed in the body after this has been injected and being already oxidized it is stable It is given in doses about one tenth of those used when giving neoarsphenamine

Mapharside is a simpler compound than neoarsphenamine having one benzene ring

It was one of Ehrlich's original compounds but he discarded it because he believed it to be too toxic It is in fact less toxic than arsphenamine because it is more rapidly excreted its excretion is completed in two days as compared with 5 to 7 days of arsphenamines.

The advantage of this drug is that its 60 mgm equal 600 mgm of neoarsphenamine The arsenic content [illegible]

toxic for experimental animals than mercury The MLD for mice is 143 mgm per kilo *and for rabbits* 100 mgm when given intravenously In rats showing a trypanosome count of 150 000 to 250 000 per ccm of blood temporary sterilisation could be effected with doses of 6 mgm and permanent sterilisation with doses of 8 to 12 mgm per kilo Mice infected with the spirochætes of relapsing fever were sterilised with 10 6 *mgm per kilo and rabbits* inoculated with syphilis were cured with 23 5 mgm per kilo given intravenously

Salvarsan has the disadvantage of having an acid reaction in solution and therefore has to be neutralised at the time of use For this reason it has been replaced by neosalvarsan A solution which is not fully neutralised or the heart Neutralisation is best effected caustic soda solution to precipitate the base a little 0 5 per cent saline and then add (about 0 6 ccm in all) finally dilute to 300

(vi) Neo arsphenamine

Synonyms —Neo salvarsan Neo kharsivan Ehrlich 914 Novarsenobenzol Novarsan Novarsenobillon Metarsenobenzol Neo-arsenophenolamine, Sodium dioxy diamino arsenobenzene methanesulphonate

This is a condensation product of salvarsan It differs from salvarsan in that it is not a combination of dioxy diaminoarsenol benzol with HCl but with *sodium methane sulphonate It consists chiefly of sodium 3, 3 diamino-4 4* dihydroxy arsenobenzene N methanol sulphoxylate It is a yellow powder readily soluble in water, giving a neutral solution It is a stable preparation and readily *dissolves in water forming a neutral solution it can therefore be injected intra* venously in concentrated form The dry powder must contain not less than 10 per cent or more than 21 pe ... that *during the first 10 hours eve* spirochætes but after 15 hour eventually all are destroyed *200 000 as compared with 1 in*

When injected intravenously into times less toxic than salvarsan The product in rats is 254 mgm per kilo b rabbits it is 200 mgm when given intravenou *dose of neo salvarsan for rats infected with* muscularly and for rabbits inoculated with The hydrogen ion concentr as that of the blood while ...on of salvarsan is more than 9 It therefore ... in the blood and *tissues*

... the ... hich ... n is ... gm ... rsan ... is 6 to 8 intravenous injections ... arly cases the first 2 or 3 injec ... atient is allowed 6 to 8 weeks' rest and then another course is given and this in early cases may be repeated till 3 or possibly 4 courses have been given The drug is combined with bismuth preparations

tolerated dose increased as the duration of treatment increased and since the curative dose was constant the margin of safety increased with duration Eagle & Hogan considered that any desired margin of safety could be achieved by *prolonging the period of treatment*, i e from intensive course of 5 days which was dangerous to prolonged course of 18 months which was vexatious

The single weekly dose of mapharside is 1 mgm per kilo of body weight for adults The usual single dose for average adults is 60 mgm (0 06 gm) Regard less of the treatment method used the total curative dose of mapharside for adults *with early syphilis ranges from 1 200 to 2 400 mgm* *Clinical results with* all theraputic routines now in use (five days to eighteen months) are about the same provided the total dose of mapharside is at least 1 200 mgm

Infants and children tolerate mapharside satisfactorily Initial doses should be on the basis of 0 5 mgm per kilo of body weight The maximum dose of 1 mgm per kilo may be administered weekly during regular courses thereafter

Mapharside is said to have the lowest record of toxicity of any trivalent arsenicals used in the therapy of syphilis Serious nitritoid crisis has not been reported Mild cases of dermatitis may occur, although the incapacitating exfoliative type is very rarely encountered Reactions most frequently observed have been transitory nausea vomiting lacrimation and pruritus Of these the gastric symptoms are the most troublesome *The low toxicity and high clinical* effectiveness was recognized by the National Research Council (U S A) in 1941 They concluded that 'the preferred arsenical in and out of hospital is mapharside When mapharside is not available Neoarsphenamine may be used

Silver salvarsan or silverarsphenamine is a metallic arsenobezene compound It is a br wnish black powder read ly soluble in water giving an alkaline solution It contains not less than 19 0 per cent of arsenic and 12 to 14 per cent of silver *It is given intravenously* in doses of 0 1 to 0 2 gm for women and 0 25 gm for men at weekly intervals

n l of neo sal arsan

(viii) Sulpharsphenamine

Synonyms —Sulfarsenol Sulpharsenobenzene Myosalvarsan

This was originally a French pre aration It is a fine yellowish powder which dissolves easily in water giving a neutral or intramuscularly It contains of sulphur Chemically it is 0 12 to 0 18 gm for the first inj t 0 45 to 0 6 gm For intram dissolved in 0 3 ccm of freshly 2 0 ccm There is less rea tior

For intravenous injections 0 06 gm is dissolved in 6 0 ccm preferably 20 ccm or more of double distilled pyrogen free water Harrison (1921) does not recommend the intravenous use of the drug as dermatit s and other untoward effects are more l kely to follow by this route The MLD (minimum lethal dose) of th s drug in white rats ranges from 320 to 480 mgm and the MED (minimum effective dose) from 15 9 to 31 5 mgm per kilo when given intravenously When given intramusc he MLD is 400 to 700 mgm and the MED is 15 6 to 34 mgm efficiency treatm ypodermic usef with veins as 20 untoward ents ons It is is specially well tole e by c congenital

syphilis Dermatitis and jaundice may be produced by it, but acute symptoms such as nausea, vomiting and diarrhœa are less common the incidence of general reactions is also lower Harrison (1923) recommends it when myocarditis and aneurysm are present. Patients receiving sulpharsphenamine should be carefully watched as there is higher incidence of reactions than other arsenicals Those met with are —dermatitis, hæmorrhagic eruptions meningo-vascular reactions, and aplastic anæmias. The drug is sold in ampules containing 0.1, 0.2, 0.3 0.4, 0.5, 0.6 and 0.9 gm.

(ix) Other Arsenical Compounds

Thiosarmine or disodium-dioxy-diamino-arsenobenzene methylene sulphonate has been prepared in the Brahmachari Research Institute, Calcutta It is very closely allied to other sulpharsenobenzene compounds such as sulfarsenol, kharsulphan, sulpharsphenamine, etc

Thiosarmine is a light yellow powder readily soluble in water almost neutral in reaction and having a hydrogen ion-concentration of 7.2 to 7.4 It is fairly stable and does not change its colour even on standing for 48 to 72 hours When heated it decomposes without melting The arsenic content varies from 19.5 to 25 per cent

Toxicity The toxicity of the compound is low Given intravenously in white rats the maximum tolerated dose of thiosarmine was 300 mgm and the minimum lethal dose 490 mgm per kilo of body weight The minimum lethal dose in the author's series of experiments, when given intravenously in a 2 per cent solution in white mice was found to be between 425 to 450 mgm per kilo of body weight

[illegible]

and cooled A 10 per cent solution is slowly injected intramuscularly in the gluteal region. It can also be given subcutaneously or by the intravenous route.

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of a [illegible]
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powder freely soluble in cold water The arsenic content of the preparation ranges from [illegible]

arsenicals and there is pain at the site of injection.

Dosage —The initial dose is 0.1 gm and succeeding dose 0.2 gm The drug is dissolved immediately before injection in 1 to 2 ccm of a sterile aqueous solution of 0.25 per cent, butyl sulphate Weekly doses are given at first later on biweekly injections may be given

Mode of action of organic arsenicals.

Mode of action of organic arsenicals Ehrlich's original idea was that these drugs had a simple parasiticidal action and that certain chemical chains in the drugs had a selective chemical affinity for certain side chains in the protoplasm of the organisms and therefore the organisms were killed without harm to the host, this idea has now been given up That organic arsenical compounds are converted into trivalent oxides before parasiticidal action [illegible]
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immediately after injection. The compounds of R.As=As.R. (salvarsan) type in similar doses have little action on trypanosomes for the first hour and do not kill 90 per cent of the parasites after 2 or 3 hours. It seems that it is the persistent effect of minute quantities of the oxide, far below the concentration immediately lethal in vitro maintained for sometime, which is responsible for cures.

tolerated dose increased as the duration of treatment increased and since the curative dose was constant the margin of safety increased with duration Eagle & Hogan considered that any desired margin of safety could be achieved by prolonging the period of treatment, i e, from intensive course of 5 days which was dangerous to prolonged course of 18 months which was vexatious

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[illegible] ompound of neo salvarsan

with 167 mgm of silver salvarsan and 370 mgm of neo salvarsan These compounds have the same actions as the ordinary compounds

(viii) Sulpharsphenamine

Synonyms —Sulfarsenol Sulpharsenobenzene Myosalvarsan

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For intravenous injections 0 06 gm is dissolved in 6 0 ccm preferably 20 ccm or more of double distilled pyrogen free water Harrison (1[illegible]

[illegible]

ilo body weight It is equal in efficiency syphilis when given by the hypodermic hildren and for obese persons with veins difficult to find such strong solutions as 20 to 30 per cent can be given without untoward symptoms The drug is useful in patients who develop shock or nitritoid reactions It is therapeutically just as effective and is specially well borne by children with congenital

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0.1, 0.2, 0.3, 0.4, 0.5, 0.6 and 0.9 gm.

(ix) Other Arsenical Compounds

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The dosage recommended in syphilis

Bismarsen or bismuth arsphenami

than the summation of these two drugs separately The drug is slower in action than the arsenicals and there is pain at the site of injection.

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Mode of action of organic arsenicals.

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the organisms and therefore
ea has now been given up
That organic arsenical compounds are converted into trivalent oxides before parasiticidal

render trypan
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that arsphenamine should be injected at intervals of five days or less instead of waiting fo the customary week. The organisms should be attacked with fresh drug when their vital r is lowest so that they may not multiply or develop resistance.

These drugs are examples of compounds whose therapeutic efficiency is due to change

compounds

(5) Toxic Effects of Arsenic Compounds

Inorganic arsenic, when taken by the mouth in large doses produces severe gastro intestinal irritation vomiting painful profuse watery diarrhœa (rice water stools) suppression of urine, intense thirst, prostration and collapse, even when given hypodermically the drug produces its action on the epithelium of the gut producing fatty degeneration, necrosis and ulceration The symptoms usually appear within half to one hour after it is taken by the mouth In fulminant cases, the accumulation of blood from the general circulation into the splanchnic area on account of capillary paralysis may produce collapse and death without producing any of the usual symptoms At the post mortem the stomach and intestines are found inflamed and there are patches of softened mucous membrane. If the patient survives long enough, fatty degeneration of the liver, kidney and heart is seen

Fatal doses of white arsenic vary with the solubility of the preparation Five to 50 mgm of the trioxide produce toxic symptoms, while 0 1 to 0 3 gm are fatal but recovery may occur after much larger quantities

Chronic poisoning The symptoms which appear first are loss of appetite ... l neuritis ... *nd patchy* ... lysis may ... sensation may be dulled and blindness may be produced The endothelium of the capillaries later the intestinal epithelium and finally the cells of such organs as the liver kidneys and the heart undergo fatty degeneration Arsenic is quickly absorbed and is slowly excreted it is therefore a cumulative poison Pigmentation of the skin dermatitis and peripheral neuritis commonly occur in chronic poisoning

Treatment of arsenic poisoning Acute arsenic poisoning is usually fatal and therefore treatment should be started as early as possible Elimination of the drug by emetics lavage *with warm water or purgation should be tried at the first* instance Chemical antidotes are not of much value Ferric hydroxide with

magnesium oxide was long considered the best antidote the ferric hydrate and arsenic forming an insoluble compound It is now known that the antidote is

evacuation

Chronic arsenic poisoning does not require prompt and energetic treatment The administration of arsenic in any form should be stopped Rest in hygienic surroundings a milk diet and alkalies are indicated Symptomatic measures against vomiting diarrhœa etc and stimulants whenever necessary may be exhibited

Toxicity of organic compounds Organic arsenicals such as salvarsan and its substitutes are usually injected in doses as high as can be tolerated and there fore toxic effects are not uncommon These are generally due to three causes, in order of importance they are—

1 *Pathological states and susceptibility of the patient* Fear nervousness

ves produced by syphilis non

t part Natural or acquired

important factor

2 *Errors in method of administration* Failure to make proper solutions *e g* making them over acid or over alkaline, use of defective saline solutions excessive dilutions rapid intravenous injections oxidation of the solution emboli of the undissolved drug cotton air etc are factors of some importance

3 *Properties of the drug itself* The solutions may have toxic physical properties agglutination of erythrocytes or precipitation of plasma may occur or hæmolysis may be produced Oxidation of the drug may occur or toxic impurities may be present

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often

be 1 in 63 000 if the dosage was below 0 6 gm and 1 in 3 000 if it was above. The danger can be reduced by using a reliable drug proper technique and careful examination of the patient The symptoms may be divided into three groups

(i) Immediate, early and late reactions

A *Immediate reactions* In the great majority of cases after intravenous injection of neo salvarsan and sulfarsenol by the technically correct method no untoward effects are noticed The first effect mentioned by the patient is a peculiar odour and metallic taste This effect is probably due to the circulation

the other symptoms are as a rule absent The more severe immediate reactions are as follows—

A new conception of the arsphenamine treatment of syphilis is offered by Anwyl-Da
Whil
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that arsphenamine should be injected at intervals of five days or less instead of waiting
the customary week. The organisms should be attacked with fresh drug when their vital
is lowest so that they may not multiply or develop resistance.

These drugs are examples of compounds whose therapeutic efficiency is due to chan
which take place in them in the body. Their therapeutic efficiency is estimated by determ
ing the ratio between the sterilising dose and the tolerated dose though this is liable
species of trypanosomes and also of the anima
anced the theory that arsenic in the form
and is a specific poison for the sulph hyd
nd possibly other SH compounds present
one group is concerned in the oxidation a
reduction processes in the living cells. Arsenic therefore in the form of an aroma
arsenious compound may be regarded as a specific poison which acts by combining wi
the SH compound in the protoplasm and its effects can be counteracted by introducing t
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Although the symptoms described are very alarming they are rarely fatal Cases of cardiac syphilis with aortic insufficiency and myocarditis are specially liable to develop alarming symptoms with sudden syncope after arsphenamine In these cases cold sweats gasping respiration pallor bradycardia and low blood pressure are associated with acute cardiac damage

Various explanations have been suggested to account for the immediate vasomotor disturbances As adrenalin relieves those symptoms it was thought that insufficiency of the adrenal glands might be the cause Another explanation is that a precipitate is formed None of these hypotheses are supported by ex perimental data The theory most favoured is that the symptoms resemble anaphylactic shock and many of these certainly seem to be those due to liberation of histamine and histamine like substances

Treatment

Treatment The symptoms are prevented by slowness of intravenous injec tion and by injection of 0 5 to 1 0 ccm of adrenaline hydrochloride 1 1 000 A useful preventive of immediate reaction is to dissolve the dose in 2 0 ccm of water and the solution added to 8 ccm of 50 per cent solution of glucose If symptoms appear the patient is made to lie flat and adrenalin 0 5 to 1 ccm of a 1 in 1 000 solution is given intramuscularly at once or it may be used as a prophylactic before the injection Pituitrin may be given with adrenalin or by itself atropine sulphate 1/50 gr subcutaneously relaxes the bronchi and relieves dyspnœa In severe cases of coma give adrenalin intravenously Ephedrine is said to be specially useful in preventing vasomotor paralysis Fractional injec tion *i e* 1/10 of the dose an hour before the full dose may be adopted as a prophylactic measure In animals injection of cæsinum eosinate prevents the symptom of anaphylactic shock and 15 ccm of a 6 per cent solution prevents shock in man neoarsphenamine may be dissolved in this solution Sometimes symptoms of increased cranial pressure or tension headache occur In these cases magnesium sulphate should be given internally or by rectal enemata to produce dehydration If symptoms of encephalitis appear the pressure may be relieved by drawing cerebro spinal fluid and adrenalin may be given

B *Early reactions* These generally start in 1 to 4 hours but may occur within 24 hours after injection There is fever headache protein or colloidal shock accidents of injection such as phlebitis and thrombosis also come under this heading The kidneys may be involved and albumin and casts may be found in the urine Temperature rarely exceeds 101°F There is evidence that fever enhances the antisyphilitic effects of the remedy and some authorities give pyretic injections a few hours after the arsenicals Gastro intestinal symptoms occur if injections are given soon after a meal These are nausea vertigo headache thirst vomiting and diarrhœa Symptoms usually stop in 12 to 24 hours but may continue for several days Urticaria during and immediately after the injection is comparatively rare Herpes labialis and occassionally herpes zoster may occur Adrenalin is also beneficial in these cases Protein or colloidal shock produce fever perspiration chilliness or even a rigor

C *Late reactions* These occur from one day to several weeks after the inject on These are hæmorrhagic encephalitis dermatitis neuritis Herxheimer's reaction and jaundice Hypersensitiveness to these reactions may be acquired It is not infrequently seen that patients who have one or more courses of arsenical compounds suddenly or gradually begin to develop immediate or early toxic react ons after small doses *e g* nausea vomiting flushing occurring immediately after injections The skin tests are negative so that the effect is not cumulative.

1 Acute *physico-hæmoclastic reactions* occur with salvarsan solutions and these are due to errors in neutralisation and the symptoms are the result of widespread embolism and infarction, especially of the lungs and cardiac dilata

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in the chest occur due to emboli in the lungs, convulsions may occur due to emboli in the brain no demonstrable symptoms are produced by embolism of the liver spleen kidney and other organs Broncho pneumonia and pulmonary embolism may develop after an interval The patient becomes anxious expresses a fear of approaching death coma may follow from cerebral anæmia The patient may recover within ½ to 2 hours or die The cause of this acute crisis is unknown though coagulation of the blood proteins has been suggested There is no evidence to support this but *agglutination of red blood cells may occur in vivo* as a result of injection of solutions of arsphenamine and multiple emboli have been noted in the lungs

The treatment in these cases is to lay the patient flat on his back and to give 1 to 2 minims of 1 in 1 000 solution of adrenalin intravenously for less severe reactions give 0 5 to 1 0 ccm intramuscularly Atropine sulphate 1/50 grain may be given intramuscularly for stimulating the circulation Intravascular agglutination can be prevented by injecting arsphenamine with a protective colloid such as gelatine.

2 Acute vasoparetic reactions or nitritoid crises so called by Milton

sympathetic system but it is more likely that they are due to the toxicity of t drug or abnormal changes in the capillaries or a combination of the two The symptoms occurring immediately after or during injection are flushing of the face, dilatation of the pupils increased pulse rate and dimness of vision There may be pain in the gums and teeth In more severe cases the lips and tongue become swollen there is a feeling of constriction in the throat and upper part of the chest and dyspnœa a tingling sensation in the extremities congestion of the conjunctiva and lachrymation are always present The patient may fall if standing when the reaction comes on In still more severe cases there may be urticaria either limited to portions of the body or generalised over the limbs and trunk profuse perspiration vomiting retching loss of sphincter control and possibly loss of consciousness which may last several hours These symptoms though rare occur in a certain percentage of cases after each injection Silver salvarsan unless injected very slowly almost always causes vasomotor symptoms The face becomes pale the pulse feeble and vomiting may ensue In another type of reaction rigors and headache occur it is more common after the first

Occasionally vomiting is followed by severe diarrhœa

Herpes labialis may occur In mild cases the

fright The symptoms can all be explained by

els especially the capillaries Extreme cerebral

occur causing apoplexy In mild cases there is only headache and vomiting and these soon pass off Usually symptoms pass off in an hour but exceptionally may persist for several hours Syncope may be a prelude to vomiting The patient should have no solid food two hours before injection

Although the symptoms described are very alarming they are rarely fatal Cases of cardiac syphilis with aortic insufficiency and myocarditis are specially liable to develop alarming symptoms with sudden syncope after arsphenamine In these cases cold sweats, gasping respiration pallor, bradycardia and low blood pressure are associated with acute cardiac damage

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Herxheimer's reaction These are of ...

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These reactions can be prevented by giving the drugs in small doses during the first 24 to 48 hours This type of reaction has been attributed to liberation of ectic toxin from spirochætes killed by drugs The luetic lesion especially of the trunk, show bright red erythema lasting a few days Generally they cause little inconvenience, but analogous reactions in cerebral and hepatic gummata may be dangerous

Cerebral symptoms Hæmorrhagic encephalitis occurs especially after large doses or when *ordinary doses are given in qu ck succession* The symptoms start 2 to 5 days after injection with severe headache vomiting weakness œdema of face muscular twitching dyspnœa epileptiform convulsions clon c spasms and suppression of urine Loss of deep reflexes a positive Babinski sign and continued convulsions are some of the signs of involvement of the central nervous system Post mortem examination shows numerous *small hæmorrhages but no evidence of softening of the brain tissue the capillaries are* filled with hyaline thrombi The lungs spleen and kidneys are all congested but free from thrombi Arsenic is said to be responsible for the production of these symptoms. Hæmorrhagic encephalitis however commonly occurs in the second stage of syphilis. In a few cases it has occurred after a single injection of arsenicals but in the majority of *cases after the second inject on Examination of the brain may show the presence of arsenic* or not The ætiology of hæmorrhagic encephal tis is probably the same as that of the acute vasoparetic reaction following injection of arsphenamine.

Dermatitis and allied reaction These are the most annoying of all reactions and consist of rashes on the skin and mucous membranes They are less common with organic compounds and their characters depend chiefly on the sensitiveness of the patient to the drug the amount of arsenic given and the degree of skin reaction The most common types are patches of urticaria erythema and rarely
The eruptions generally subside in a day or two
days after admin stration especially after intraven
action may turn into exfoliative dermatitis which
its appearance in about 30 per cent of cases V
that an initial urt caria or discrete erythema may become a confluent erythema in 24 to 48 hours later it may turn vesicular and subsequently pass on to exfoliative dermatitis Arsen cals should therefore be discontinued if signs of skin irritation appear Kolmer has classified *these reactions into 4 groups*

1 Mild and early skin lesions consisting of simple erythematous rashes urticaria, herpes pruritus These may be due partly to colloidal phenomena and partly to liberation of spirochætal endotoxins—Herxheimer's reaction

2 Severe and late skin lesions consisting of dermatitis and purpura. The former may consist of scarlatiniform erythema with desquamation, erythema multiforme (papular and vesicular), lichenplanoid or with acute exfoliation which may be simple rheumatic or hæmorrhagic

3 *Mucous membrane* lesions consisting of stomatitis exfoliative ileocolitis conjunctivitis, *vaginitis and broncho pneumonia*

4 Chronic and recurrent skin lesions such as fixed arsenical rashes pigmentation and argyria, melanosis hyperkeratosis of the palms and soles of the feet may develop

Forms of eruption 1 *Erythema* This may vary from mild redness to deep redness
... appears first on the flexor surface of the limbs
is either morbilliform or
a copaiba rash. The rash
more common it may be
the formation of ves cles

... preceded by an acute erythematous dermatitis and in
tration is more notice-
rupture thus produc
exfoliation crusting

and scabbing from the drying exudate The whole body may be uniformly affected or exfoliation may be confined to certain parts especially the ears scalp armpits groins and fold of the skin There is œdema of the eyelids conjunctivitis and photophobia. Fever headache faucial congestion and emaciation are present. Secondary infection may take place There may be loss of the hair of the scalp eyebrows and eyelashes. The main complications are glandular enlargement, abscess formation in the groins broncho-pneumonia, œdema of the lungs exfoliative vaginitis Albuminuria may be present When recovery occurs convalescence is protracted the skin becomes thin and atrophic and assumes a brown tint

3. *Chronic skin lesions* Fixed arsenical exanthemata develops by the production of urticarial patches in the same situation leading to an elevated smooth plaques. Raynaud's syndrome with gangrene has been recorded Fibrosarcoma at the site of injection of arsphenamine has occurred.

(h) Treatment

Most cases of arsphenamine dermatitis present warning signs before the generalised dermatitis begins In early cases, the treatment with arsphenamine should be guardedly continued by changing to a different type of arsenical smaller doses, etc, before true allergic state develops Physiologic solutions of sodium chloride, dextrose, gelatin sodium thiosulphate and calcium have been added to the arsphenamine to render it less toxic. Clinical experience has proved that sodium thiosulphate is a very valuable detoxicating agent Its mode of action is unknown but probably it transforms arsenic into a less toxic, more efficient and a more easily excretable product On the other hand, some authorities believe that owing to the presence of the sulphydryl group sodium thiosulphate changes the insoluble arsenic compounds developed in the skin into soluble forms In order to avoid arsenical dermatitis it is advisable to combine sodium thiosulphate with arsphenamine But once the dermatitis has set in sodium thiosulphate fails to hasten the resolution, its value only lies in its use early in the disease Fifteen grains (1 0 gm) of sodium thiosulphate by the mouth 3 or 4 times a day is said to produce good results, but [illegible]
10 per cent solution starting [illegible]
1 8 gm on successive days [illegible]
doses twice daily in 120 to 2 [illegible]
act by releasing the arsenic deposited in the skin and along the nerve trunks [illegible] The excretion of arsenic is accelerated, [illegible] disappears and the pigmented areas [illegible] is due in some cases to a saturation [illegible] the treatment, or to arsenic-fast or mercury fast strains of spirochætes In such cases sodium thiosulphate produces excellent result A series of biweekly intravenous injections for 5 to 7 weeks. [illegible]

Wassermann fast syphilis

Thiosinamin has also been recommended intravenously in 3 grain doses in 10 ccm of sterile water but it may produce digestive *disturbances lassitude and* fever Intramuscular injections of intramine in doses of 2 5 ccm of a 1 0 per cent emulsion are beneficial, as many as 12 injections may be given.

Liver therapy Based upon the hepatotoxic theory, some workers have used injections of liver extract *in the treatment of* arsenical dermatitis with good results It is given in doses of 5 to 10 ccm intramuscularly, three times a week. The therapy stimulates the disturbed function of the liver, *cures chronic arsphena* mine intoxication and prevents further manifestation of arsphenamine sensitisation.

the bone marrow and broncho pneumonia with a poor cellular reaction

Syphilitic and arsenical jaundice The intensity of jaundice may vary from a transitory jaundice to acute yellow atrophy of the liver It may be early or benign, late or severe, and lastly acute yellow atrophy may result Early jaundice commences within a few days, sometimes within a few hours of the injection *It may come on after the first injection or after any subsequent injections There* may or may not be any constitutional disturbance but that does not mean that the liver has not been damaged Cases have been recorded with initial transient jaundice but some months later the patient has died of acute yellow atrophy of liver Late jaundice is a very serious condition It is accompanied by fever and usually occurs after many injections (one or two courses) and is believed to be more commonly caused by neo salvarsan though there are no data to support this belief Jaundice is generally intense and unless there is acute *yellow* atrophy of the liver the patient may recover In the late type of jaundice The jaundice *from the* mptoms of acute hepatic l other nervous symptoms s classified jaundice into four groups according to its ætiology

...neration hepatitis or obstructive jaundice he liver can be shown by the lævulose *ice structural alterations, and the phenol* cy after a series of doses or courses. atrophy is the long latent period usually iset of symptoms *With trinitrotoluene*

2 Due to syphilis alone *This may be mild or severe and the pathological changes* are perihepatitis diffuse hepatitis or gumma

3 *Due to arsenic and syphilis.* This is considered to be a form of Herxheimer's reaction syphilitic infection of the liver is intensified as a result of administration of arsenicals Arsenicals may also stimulate a bacterial infection of the liver

4 The immediate predisposition to jaundice is neither due to arsenic nor syphilis of liver but in the majority of cases to summation of the changes produced by the disease and the arsenicals, *and it* is possible that the administration of mercury may help in intensifying the hepatic damage.

Prevention and Treatment of jaundice Rest in bed mild laxatives carbohydrate diet which increases the resistance of the liver, with no fats and little proteins are recommended Milk may be given and the patient is advised to

drink plenty of water When jaundice is clearly due to syphilis, give anti-syphilitic treatment with arsenicals mercury or bismuth compounds, but if due to arsenic injections these should be immediately stopped Intravenous injections of sodium thiosulphate, thiosinamine or contramine (diethyl dithiocarbamate) have been recommended

Meirowsky (1920) showed that when the dose of neo salvarsan exceeded 0 6 gm the death rate went up considerably and hence he recommended 0 6 gm to be the maximum dose The death rate was much less with neo salvarsan than with salvarsan Strong solutions of salvarsan and sulfarsenol are directly hæmolytic *in vitro* for washed corpuscles but they are much less so in the presence of serum and intravascular hæmolysis is not therefore very likely to occur

Nervous reactions

Nervous reactions Numbness of the fingers and the soles of the feet may occur As these symptoms frequently forecast the onset of dermatitis the injections should be stopped As a rule these are not accompanied by pain but this may occur and polyneuritis may be produced followed by paralysis Neoarsphenamine is said to have produced more cases of paralysis than arsphenamine Sometimes injections are followed several weeks or months later, by severe nervous manifestations *e g*, epileptiform convulsions They occur also with mercury and Ehrlich suggested that they are due to incomplete destruction of the parasites The optic and auditory nerves are not affected by trivalent compounds but atoxyl and tryparsamide (pentavalent compounds) produce retrobulbar neuritis and transient dimness of vision or amblyopia Arsenicals with an amino group or a substituted amino group in the para position to the arsenic *e g*, atoxyl, produce optic atrophy in the rabbit Organic arsenicals with the amino group in the ortho or meta position to the arsenic on the other hand produce no optic atrophy Herxheimer's reaction occurs in secondary syphilis especially if large doses have been given, small ascending doses of these compounds do not produce it

Summary

Summary The toxic symptoms produced by injections of organic arsenicals may be briefly classified as follows —(1) Those occurring immediately *e g*, flushing of the face headache lachrymation œdema, dyspnœa swelling of

sness and

ing within

tempera

s dilation

of the pupils, loss of reflexes, coma and rarely death In addition there may be eruptions on the skin exfoliative dermatitis (complicated with broncho pneumonia and septicæmia) jaundice (early, late and acute yellow atrophy) epilepsy or hæmorrhagic encephalitis Acute yellow atrophy often supervenes on late jaundice Rare lesions are acute hæmorrhagic nephritis ulcerative enteritis and aplastic pneumonia (4) Complications now regarded as relapses of syphilis are due to spirochætal toxins suddenly liberated These include affections of the nervous system, deafness cranial nerve palsies, etc

Pathological changes produced by organic arsenicals These changes were studied in animals The type of

compounds some being

arsenic constituent and

tion and minute hæmor

If death occurs at on

of the brain and meni

bosis and plasma precipitates Small capillary hæmorrhages are found in some organs but degenerative lesions are not produced unless the animals survive a few days In human subjects where death occurs within 24 hours after accidental administration of acid solution

of salvarsan advanced degenerative les ons are found in the l ver kidneys and other organs The majority of deaths in human subjects have occurred after several doses hav been given death be ng due to chron c rather than acute poison ng In Europe sal arsa fatal t es are mostly ascribed to hæmorrhagic encephal t s but in the Un ted States they have been put down to degenerat ve changes in the l ver and kidneys

nd *Cautions and contra indications* The only real contra indication is hyper sensitiveness to arsenic Individuals who develop acute reactions dermatitis and jaundice are bad risks and in these cases other drugs should be tried Somet me the substitution of one compound for another may avert such reactions In minor cases of dermatitis if a beginning is made with a small dose and it is gradually increased severe reactions may be avoided A sharp look out must be l ept for urticaria fleeting erythema itching of the palms etc as these give a warning that more severe reactions may follow Cases of jaundice are also bad risks and very great care should be taken in giving arsenicals if previous injections have caused it

Organic arsenicals should be given with caution in cases of emaciation malnutrition in diseases of the heart and blood vessels (syphilitic aortitis and myocarditis) in tuberculosis with hæmoptysis in affections of the brain and meninges in advanced cases of diabetes and nephritis and in old and feeble persons of very advanced age Arsenic should not be given where vitality is very low as a result of acute manifestations of syphilis In syphilis of the optic nerve pentavalent arsenicals should never be given while trivalent compounds should only be tried in small and ascending doses According to some authorities tryparsamide may be given safely when the optic nerve is diseased provided the doses are small and carefully regulated

of ns *Prophylaxis of toxic reactions* The measures taken have been divided into three groups

1 *Those referable to the patient* Allay fear and nervousness if constipa tion is present it should be relieved the injection should be given on an empty stomach preferably in the morning the urine should be examined previously in

and bismuth are also be ng tried the functional

ted in selected cases The first dose should be

se this tends to increase the tolerance of the

individual In long standing cases give mercury or bismuth first or very small doses of arsenicals to prevent Herxheimer's reactions In women the injections should not be given during the menstrual period and special care should be exercised wher pregnancy exists as abortion may take place When giving pentavalent compounds special attention should be paid to the eyes to guard against toxic amblyopia The injections should be given deep into the muscles and not ii [illegible] ptoms

1/100 to [illegible] e the

main injection [illegible] efore

the injection prevents acute vaso paretic reactions Adrenalin is the most useful drug to cope with nitritoid crisis Injection of calcium salts either prior to or in conjunction with salvarsan or neo salvarsan injections is sa d to prevent the toxic effects of the drug Calcium chloride dissolved in distilled water is usually given intravenously but it may also be admin stered orally

2 *Those referable to the preparation and administration of solutions* Use freshly distilled water or sal ne free from organic matter For dilute solutions (50 ccm or more) use 0 5 per cent saline in preference to water Filter all solutions After neutral sation allow *arsphenamine solutions* to stand for 10 to 20 m nutes before inject on Injections should be given slowly New rubber tubing should be avoided

3 *Those referable to the drug* Avoid products over two years old and all cracked ampules should be thrown away If there is suspicion of a crack dip the ampoule in alcohol which will find its way in if there is a leak Before injection carefully verify the drug which is going to be injected Solutions should never be given unless they are brilliantly clear, cloudy solutions produce abdominal pains and immediate syncope If necessary they should be filtered

Keeping properties and media for solution Salvarsan and the allied compounds should be kept sealed in ampules in vacuo It is better to use fresh rather than old specimens The Hygienic Laboratory of U S A has placed a limit of six months on them from the date of preparation Freshly distilled water should be used for making solutions When concentrated solutions of neo-salvarsan are employed they should be dissolved in distilled water A 5 per cent solution of glucose as a medium for dissolving these compounds reduces the toxicity by preventing oxidation in solution at the same time it does not reduce their therapeutic activity Neo salvarsan and sulfarsenol are best dissolved in cold water It has been clearly established that concentrated solutions (0 9 gm in 2 ccm) of neo salvarsan and sulfarsenol do not do any harm when given intravenously It has been pointed out that shaking the solution in air even for a few seconds increases the toxicity of all these compounds by oxidation but if contact with air is prevented by means of stoppered bottles solutions may be safely kept for a few hours before injection some say they may be safely kept for 24 to 48 hours Excess of alkalinity or acidity of the salvarsan solution are both dangerous

Keeping properties and media for solution

7. Bismuth and its Derivatives

Bismuth compounds were used as cicatrising agents in the treatment of cutaneous lesions as early as the 17th century and towards the end of the 18th century they were given internally for gastro intestinal disturbances, bismuth oxide was used for dressing wounds and ulcers Robert and Sauton (1916) tried bismuth preparations in the treatment of spirochætosis of fowls and found them to be effective Sazerac and Levaditi (1921) found that in experimental syphilis of rabbits bismuth compounds had a well marked curative action They tried intramuscular injections of tartro bismuthate of sodium and potassium in syphilis in man and found that though the injections were painful the drug

Further trials showed were inhibited and early intramuscular injections

of bismuth

These findings led gradually to the introduction of bismuth in the treatment of syphilis As an adjunct to the arsenobenzene derivatives bismuth is now recognised as a drug of considerable value and has replaced mercury in the chemotherapy of syphilis

(1) Pharmacological Action



External Soluble bismuth salts are not used externally The insoluble basic bismuth salts are largely used as dusting powders on inflamed or irritated surfaces Their action is mainly mechanical as protective drying and dusting powders. Applied to wounds they dry secretions form a protective covering and exert an astringent and antiseptic action. Sometimes absorption from the wounds and raw surfaces may be very rapid giving rise to symptoms of poisoning

External

Internal Bismuth compounds have the reputation of being antacids This effect is partly due to diminution of gastric secretion and partly to neutralisation of the gastric acidity In the intestines both the subnitrate and the subcarbonate neutralise the sulphides of alkali metals and hydrogen sulphide which produce irritation and increased intestinal peristalsis these bismuth salts thus act as gastro intestinal sedatives in inflammatory conditions of the gut Further they are believed to coat the surface of the inflamed mucous membrane and allay irritation by preventing the irritant gases and fluids from coming in contact with the mucosa They also exert a certain amount of antiseptic and astringent effect and are therefore prescribed in diarrhœa Subcarbonate of bismuth is preferred to subnitrate as the latter is converted into nitrous acid by reduction in the intestines In the gut bismuth salts are converted into sulphide which is black in colour it may form crystals looking like hæmatin and may be mistaken for it Bismuth has been combined with other substances either in mixture or in synthetic compounds to produce insoluble compounds with enhanced protective and antiseptic actions *e g*, bismuth subgallate or bismuth salicylate but this is doubtful

Circulation and respiration After intravenous injections even in small doses there is a fall of blood pressure partly due to depression of the vasomotor centre but chiefly to the direct effect on the heart which becomes slow and irregular The respiration is accelerated at first but later depressed The blood shows a mild and temporary leucocytosis after injections of bismuth salts

Kidneys All bismuth compounds tend to increase the output of urine and thus promote their own excretion The administration of water and sodium chloride etc hastens the excretion of bismuth A high chloride dietary would therefore favour the efficiency of bismuth medication by helping the mobilisation of the metal from the tissues The diuretic *action of bismuth may be made use of in the treatment of œdema and anasarca Its action* has been found to be well sustained and useful in the removal of large quantities of fluid

Central nervous system In frogs the symptoms are those of stimulation of the spinal cord and medulla oblongata followed by depression and paralysis In mammals intravenous injections of large doses of bismuth act chiefly on the central nervous system producing violent clonic and tonic convulsions followed by short intervals during which the movements are weak and incoordinated

Absorption of bismuth Only very minute quantities of bismuth are absorbed from the alimentary canal This is shown by the fact that poisoning never results even when large doses of bismuth compounds are given by the mouth if the mucous membrane is intact If there is solution of continuity and ulcers are present the drug may be rapidly absorbed

Fate of bismuth in the body After absorption bismuth like antimony is widely distributed in the tissues of the body but in unequal amounts After intramuscular injections bismuth [illegible]

Bismuth appears to have the same distribution as other heavy metals *Owing to its* widespread distribution syphilitic lesions of different parts of the body improve after bismuth therapy

Excretion Although some bismuth is stored in the liver and other organs the greater part is eliminated by the kidneys liver and intestines only traces occur in sweat milk and tears The main channel of excretion after injection appears to be the kidney only one twelfth to one-eighth of the bismuth appears in the fæces Bismuth appears in the urine within 18 to 24 hours after intramuscular injection of trepol and excretion is continued for 20 to 25 days after a course of treatment in which 20 to 25 gm have been injected After intravenous injections bismuth can be detected in the urine in four hours Sometimes the urine when voided is discoloured or becomes so on standing In the latter case this is due to the formation of bismuth sulphide by the action of bacteria The diuretic action of bismuth salts has already been referred to

In human po soning bismuth is found mainly in the stomach and k dneys and a little in the liver Autopsy shows the cæcum adjoining col n and append x sta ned black with bismuth sulphide which is depos ted in the mucous membrane in the capillary vessels and lymph spaces The small ntest nes are clear

(2) Therapeutic Uses of Bismuth

Bismuth subnitrate and carbonate are valuable drugs in the treatment of inflammatory conditions of the intestines in diarrhœas and in gastro-duodenal ulcers They should be given in large doses 30 gr (20 gm) as a powder or in suspension by itself or in association with magnesium oxide or sodium bicarbonate on an empty stomach Bismuth compounds act well in gastralgia and hyper chlorhydria and combat flatulence In combination with alkalies they are also used as accessories to the emetine treatment of amœbic dysentery They also ameliorate symptoms of this disease by their inhibiting action on the peristaltic movements of the intestine by neutralising the alkaline sulphides and sulphuretted hydrogen present there They are used in chronic ulcers of the skin and in the treatment of deep seated sinuses The nitrate or carbonate of bismuth mixed with vaseline in 30 per cent strength is injected into tuberculous and other sinuses with the object of producing healing effects by cicatrization They are however l able to cause poisoning if the sinuses are very extensive

Syphilis The bismuth treatment of syphilis is one of the noteworthy advances of therapeutics The spirochæticidal properties of the organic and inorganic compounds of bismuth have been thoroughly tested and they are being largely used at present in the treatment of syphilis

Syphilis

Bismuth compounds are found to possess spirochæticidal activity of a very high order This will be appreciated from the fact that a concentration of 0 2 mgm in one litre of blood is sufficient to produce an antisyphilitic effect A single therapeutic dose is five times smaller than the single maximum tolerated or toxic dose *i e* the chemotherapeutic index is 5 which is very much higher than that of mercury compounds but not so high as that of the organic arsenicals

lesion and cicatrization Spirochætes d sappear from the chancre in 24 to 56 hours the chancre is healed in 4 to 10 days and enlarged lymph glands in the neighbourhood of the chancre disappear Rapid disappearance of mucous patches occurs after administration of bismuth compounds a previously positive Wasserman reaction may become negative under treatment but not so rapidly as with the arsenicals With colloidal bismuth mucous papules become cicatrized and treponema disappear after the first or second injection Headache fatigue and pains in the bones frequently cease after a few injections In the tertiary stage of the disease bismuth is also useful gummata disappear and also chronic encrusted ulcers of long standing and ulcers of the palate heal up rapidly Cases which are resistant to mercury and arsenic sometimes do better with bismuth Bismuth appears to be less effective and slower in action than salvarsan but more effective than mercury After treatment with arsphenamine no living spirochætes can be detected after 24 hours whereas after treatment with bismuth living spirochætes do not disappear for 3 to 4 days in the mucous lesions Bismuth

and in congenital syphilis That reinfection after bismuth therapy has occurred shows that the sterilization produced by it is definite Simultaneous treatment with arsphenamine is not necessary for clearing and healing of acute lesions or for sterilisation of lymph glands, as bismuth is effective by itself Combined treatment however is desirable to cut short the length of treatment and to diminish the discomfort and inconvenience of the patients The combination of bismuth with arsenicals is now preferred to the combination of mercury and arsenicals because the former is more effective

Effect on serological reactions The development of a positive reaction in case of primary sero negative syphilis treated with arsenicals is rare, but with bismuth treatment a weakly positive reaction may develop After one month's treatment of primary and secondary sero positive cases more sero negative cases are obtained with arsenicals than with bismuth preparations Cases of positive Wassermann reaction, which are uninfluenced by arsenic, are unaffected by bismuth also In congenital syphilis there is said to be more chance of the reaction becoming negative with bismuth than with arsenicals The action of bismuth is considered by some to be inhibitory rather than curative

Neurosyphilis Syphilis of the nervous system is not frequently benefited by arsenic preparations, in these cases bismuth preparations are useful Their efficiency in the neuromanifestations appears to be superior to that of the arsphena [illegible]

chief drug used in the treatment of neurosyphilis and even now it is advised by the neurologists in combination with arsenical treatment

Bismuth has established for itself a permanent place in the treatment of syphilis by reason of its low toxicity for the body associated with marked spirochæticidal properties, it is specially indicated in the treatment of acute syphilis when arsphenamine and its substitutes cannot be given *e g*, in nephritis jaundice etc *it is of value in the treatment of chronic syphilis and especially that of the* central nervous system It should be used in the treatment of syphilis in all its stages along with organic arsenicals as a form of combination therapy, which is the keynote of success in the treatment of either acute or chronic syphilis It is specially indicated in cases resistant or intolerant to arsenic.

Prophylactic effects of bismuth in syphilis The value of mercury applied [illegible]

Bismuth like mercury and arsenic is also claimed to have a prophylactic value against syphilitic infections It has been seen that in experimental syphilis bismuth acts definitely as a prophylactic and that bismuth medication protects rabbits from infection for a month or more.

Yaws or Framboesia As a result of its successful use in syphilis bismuth has naturally bee[illegible]
East Africa ha[illegible]
neo salvarsan [illegible]
in freshly prepared solutions at intervals of a week produce healing of the lesions

but a larger number will be required to eradicate the parasites Besides bismuthyl tartrates bismuth subgallate (dermatol) has been used in 3 ccm doses of a 10 per cent emulsion in oil given intramuscularly twice a week Very good results were obtained with 10 injections but this produced toxic effects On a large scale patients have been treated with a single massive dose of dermatol, only 15 per cent relapsed The author has tried *bisnene* in doses of 0 1 to 0 15 gm intravenously in a few cases with good results The results are as good as those with neo salvarsan and other bismuth preparations, it is much cheaper, more stable and costs less than a farthing a dose

Lupus erythematosus This a chronic non tuberculous affection of the skin

Bismuth salts have been used in this condition with good results Bismuth metal bismuth hydroxide bismuth oxychloride or sodium bismuth thioglycollate suspended in oil is given intramuscularly once a week The average dose ranges from 0 3 to 0 4gm Local treatment with mercury improves the condition in many cases

(3) Modes of Administration

By the mouth As already stated only very minute quantities of bismuth are absorbed from the alimentary canal The absorption is so slow and uncertain that this route of administration is not employed for the treatment of such diseases as syphilis

By the mouth

A preparation named sobisminol has been introduced which can be given by intra-muscular injection or by mouth It is given in capsules each of which contains 0 2 gm of sodium bismuthate Orally the drug is well tolerated and

It causes

This is a

Subcutaneous and intramuscular injections Subcutaneous injections of the soluble salts usually produce severe local reactions and as they have no advantage over the intramuscular route this route cannot be recommended

Subcutaneous intramuscular injections

Tartarobismuthates of sodium and potassium and metallic suspensions of bismuth are given intramuscularly with a thick needle in the superior gluteal region Injections are given alternately on either side not oftener than once a week as there is danger of cumulative poisoning

Local reactions due to muscle irritation and necrosis may follow intramuscular injections Pain and inflammation vary according to the nature of the compound used and the vehicle employed The common type is a hard and painful swelling with considerable infiltration which may sometimes suppurate The addition of 10 minims of a 2 per cent butyn solution or phenol (1/5 gr) to trepol reduces the pain effectively though an area of tenderness may be left Histological examinations five days af
cells and leucocytic infiltr
than the oily solutions
of bismuth compounds are due to purely inflammatory reactions and are less likely to be produced when solutions are made in vegetable oils such as olive or almond oil

Intravenous injection The intravenous injections of soluble bismuth salts are so toxic that they cannot be recommended The toxicity by this route is at least ten times greater than the intramuscular route

As in the case of other heavy metals agglutination and hæmolysis may occur after intravenous injections with the formation of emboli Even with such compounds as tartrobismuthates colloidal *preparations or bismuth hydroxide* reactions may be produced immediately after injections Cases of sudden death after intravenous injection of bismuth compounds with symptoms of colloidal shock have been reported *Mercury is more toxic by the intravenous route than* bismuth the maximum tolerated dose of perchloride of mercury is 0 006 gm per kilo while that of the soluble tartrobismuthates is 0 02 to 0 03 gm Some authorities have *shown that the danger of agglutination of erythrocytes is small* but bismuth may produce precipitation of serum proteins in the same way as do the arsenicals or antimonials

(4) Toxic Effects of Bismuth

The toxicity of bismuth compounds has been worked out on animals The

casts The weakness gradually deepens into complete paralysis and the animals

experiments show (1) that intramuscular injections are less toxic than intravenous injections and (2) that bismuth is most toxic for the kidneys next for the liver and relatively non toxic for the brain heart lungs suprarenals and spleen

Changes in human beings appear to be of the same nature and symptoms are similar to those produced in animals
low undesirable effects are comparative
view of the extended use of bismuth in

Symptoms After intramuscular injection of *tartro bismuthates the earliest* symptoms observed are pain in the muscles and joints accompanied by loss of *appetite and feelings* of malaise and lassitude These as a rule are not severe but in exceptional cases intense pain *in the larger bones joints and groups of* muscles accompanied by rigors fever a feeling of compression in the chest and dyspnœa may occur a few hours (12 to 24 hours) after the injection Rheumato d
ons of the nature
occur Jaundice
whom arsenicals
have produced jaundice Local irritation at the s e of muscular injection is not uncommon a lead line may occur at the junction of the teeth and gums
due to precipitation of th
and bad taste *in the m* he
tongue and in the muc he
deposition of bismuth ls

congestion and loss of nutrition and formation of ulcers Ptyalism is unusual and when present is not so severe as in the case of mercury Bismuth is less likely to produce renal irritation than mercury, and albuminuria is therefore very uncommon even after 12 to 15 intramuscular injections of 0 1 to 0 2 gm each of tartro bismuthates It is however advisable to examine the urine every week during the course of injections Herxheimer's reaction, *i e*, pain and swelling of

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hc ... not so common as with the arsenicals

Toxic symptoms produced in human beings by the oral administration of

Considerable absorption of bismuth may however take place from wounds and raw surfaces and symptoms of acute or chronic poisoning may follow Capillary thrombosis from precipitation of bismuth sulphide in the intestinal vessels has been known to occur

Intramuscular injections and injection of bismuth compounds into long sinuses some times give rise to toxic phenomen

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ore

The circulatory depression that is noticed in animals receiving intravenous bismuth does not occur after the clinical use of bismuth as an anti-syphilitic Sometimes acute reactions due to colloidal shock may occur The symptoms complained of are dizziness pallor rapid and weak pulse dyspnœa convulsions and collapse Siderosis halitosis ptyalism and gingivitis are commonly observed various skin eruptions (purpuric scarlatiniform erythematous urticarial lichenoid exfoliative dermatitis) pruritus, renal irritation and provocative Herxheimer's reactions are sometimes seen Stomatitis and gingivitis are the most troublesome symptoms

The mechanism of production of siderosis stomatitis, and allied lesions has been explained but the muscle and bone pains are more difficult to interpret These are probably due to a neuritis similar to that produced by arsenic and mercury

Treatment of toxic reactions In poisoning from large doses of bismuth compounds by the mouth, the stomach is washed out thoroughly and repeatedly and saline purgatives are administered If bismuth paste has been given in a sinus it should be removed

Treatment of toxic reaction

In case of acute poisoning due to a large accidental dose, the most dangerous lesion is tubular nephritis If this is produced intravenous injections of sodium thiosulphate are indicated As a rule muscular pains, malaise and anorexia disappear after a few injections, but if they persist and there is anæmia, loss of

For gingivitis

ite is the best

Cautions and contraindications Before beginning a course of bismuth a
he teeth, the liver func-
ny such defect, refrain
to Cleansing of the
teeth and gums during the course is important, dietetic errors should be corrected to reduce the possibility of gastro-intestinal disturbances, such as diarrhœa and colic, the appearance of large quantities of albumin and casts in the urine also calls for suspension of treatment, if albumin had been present prior to treatment soluble salts are better The urine should always be examined before starting bismuth injections and during the course In exceptional cases renal function tests may be necessary but liver function tests are not required Sometimes a general asthenia with pallor and loss of weight occurs after bismuth injections but this soon passes off.

Mode of action of bismuth compo
produce their spirochæticidal action *in*
of sodium and potassium are capable
dilutions and bring about their comple
In both these respects mercuric chloric
compounds Levaditi believes that bisr
spirochæticidal effect in this condition
and is largely dependent on the case
is no evidence to show that new compounds are formed by processes of oxidation or reduction or that bismuth increases the production of spirochæticidal antibodies It is possible that the actual destruction of the parasites is due to the union of the metal with the proteins of the parasites According to Eagle (1938-9) there is no evidence that tissue derivatives in any way contributed to the *in vitro* antispirochaetal activity of bismuth. According to him bismuth acts neither as a catalyst nor as inhibitor nor a precursor substance but acts directly on the parasite as is the case with arsenoxide

Bismuth is also used as a non specific adjuvant in intestinal amœbiasis and its main action is as a demulcent protective astringent It reduces intestinal putrefaction and hastens degenerative changes in the entamœba by altering their environment. For this purpose bismuth subcarbonate is given in doses of one heaped teaspoonful (12 gm or 3 drams) stirred up in a glass of water or milk, every four hours till improvement results It is said to coat the ulcers and affords them mechanical protection Other compounds used for this purpose are bismuth subnitrate B P and bismuth subgallate

(5) Bismuth Compounds

The compounds of bismuth proposed for obtaining systemic effects of bismuth in the ... of syphilis have been divided into following groups —

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can also be given by intramuscular ... favourably with other water soluble compounds and there appears to be no tendency to cumulative toxic effects

Dosage —It is given in capsules each representing 150 mgm of metallic bismuth two or three capsules are given three times a day with plenty of water in adults For children the dose is half or less

(2) *Water soluble compounds*

These are used in aqueous solution some of these are also used in oil

(a) *Bismosol* is potassium sodium bismuthotartrate in 10 per cent sterile glucose solution (0 1 gm in 1 ccm), it contains a preservative Bi content 35 mgm of solution. Dosage 1 ccm three times a week till twenty doses have been given Second course after one month s interval

(b) *Bismuth sodium tartrate* (contains 72 7 to 73 9 per cent Bi), 0 3 gm of drugs in 0 04 gm of benzyl alcohol in 2 ccm of 25 per cent sucrose solution (contains 11 mgm Bi), dose 2 ccm (0 03 gm) twice or thrice weekly

(c) *Thio Bismol* is sodium bismuth thioglycollate 0 2 gm to be dissolved in 1 ccm of distilled water (contains 76 mgm Bi) Dose 1 ccm 2 or 3 times weekly

(d) *Sobisminol solution* A complex orgainc compound (each ccm containing 19 5 to 20 5 mgm Bi) Dose 2 ccm intramuscularly twice weekly in adults for 20 to 25 injections

(e) *Bismocymol* (37 to 40 per cent Bi) is basic Bi salt of camphocarboxylic acid in olive oil, each ccm containing 0 125 gm of drug Mixture contain 50 mgm Bi dose 2 ccm (0 25 gm) twice weekly for eight to ten injections

(f) *Potassium bismuth tartrate* A 10 per cent suspension in peanut oil with 0.4 per cent butyn, each ccm contains 0 1 gm of drug mixture contains 66 mgm Bi Dose 2 ccm (0 2 gm), weekly

(g) *Bismuth oxychloride* A 10 per cent solution with dextose and chlorocresol in water each ccm containing 0 1 gm of drug Dose 1 to 2 ccm twice weekly

(h) *Sodium Iodobismuthite* Consisting chiefly of hydra ed Na_2BiI_5 it contains about 21 per cent of Bi Dose 1 to 2 ccm twice weekly

(3) *Water insoluble compounds used in oil suspensions*

(a) *Bismuth subsalicylate* A basic salt containing 62 and not more than 66 per cent of Bi_2O_3. A 10 per cent suspension in peanut oil each ccm containing 0 1 gm of drug mixture contains 57 mgm Bi Dose 2 ccm (0 2 gm) weekly

(b) *Oleo Bismuth* is bismuth compound (camphorate camphocarbonate butyl thiolaurate etc) suspended in olive oil each ccm contain ng approximately 0.25 gm of drug mixture contains approximately 50 mgm of Bi Dose 2 ccm once or twice weekly

(c) *Mesurol* is basic bismuth methoxy hydroxy benzoate 20 per cent suspension in sesame oil each ccm contain ng 0 2 gm of drug mixture contains 110 mgm of Bi. Dose 1 ccm weekly

(d) *Quinobine* is quinine-bismuth iodide rendered soluble in olive oil by lecithin each ccm containing 0 158 gm of drug mixture contained 30 mgm Bi Dose 1 to 2 ccm (0 16 to 0 32 gm) twice weekly

(e) [illegible]

every three days) are in use

Bismarsen is a comb nation of sulpharsphenamine and Bi it contains 12 to 15 per cent of arsenic (trivalent) and 23 to 25 per cent of Bi It is sold in ampoules and sterile di tilled water is added d rectly into the ampoule 1 ccm for 0 1 gm The solution is given intramuscularly in average doses of 0 2 gm every three or four days It is however, not so effective as neo-arsphenamine and easily gives rise to toxic symptoms

(6) Summary

Bismuth has both a spirochaeticidal and spirochaetostatic effect Best results have been obtained with intramuscular injections, those compounds which can maintain the therapeutic level of Bi in the blood as reflected by urinary excretion, probably being the best Intravenous injections are contraindicated as therapeutic doses closely approach the toxic doses Intramuscular injections are given by inserting the needle in the inner angle of the upper and outer third of the buttocks, deep down into the muscular tissue With the Syringe tip inserted into the needle the plunger is aspirated back a little to be sure that the needle is not in a vein or an artery, this will prevent venous and arterial emboli

The efficacy of bismuth compounds lies midway between the arsenicals and mercurials Combined Penicillin and bismuth therapy gives the best chance for a cure The penetration of bismuth into the nervous system has not yet been definitely demonstrated by its presence in the cerebro spinal fluid Watery

solutions as a rule, if repeated often enough (2 or 3 times a week) give rapid absorption of metal and a sustained high concentration in the blood Oil suspensions have a slower rate of absorption and concentration in blood stream thus requiring only one injection a week Certain oil suspensions however, are more quickly absorbed than others *e g*, the absorption of bismuth subsalicylate is slowest and its excretion goes on for a long time It is however, doubtful whether excretion indicates a therapeutic level

8. Mercury and its Derivatives

Mercury was the first drug to be used as a specific disinfectant for the body tissues, for it was employed in Europe in the treatment of syphilis as early as 1 500 A D, and until the discovery of arsphenamine in 1 905 it remained the only effective remedy against this disease As a therapeutic agent in syphilis it has now been entirely replaced by bismuth Mercurials have however a powerful destructive action on some of the pathogenic protozoa and bacteria and a number of new mercury compounds have been introduced in medicine during recent years

(1) Pharmacological Action

External action Mercury has a powerful toxic action on all protoplasm and mercurial compounds and for this reason are active germicides This germicidal effect depends chiefly on the concentration of mercuric ions in their solution and on the precipitation of proteins Absence of protein precipitation is important because it diminishes local irritation favours the penetration of the mercury and obviates the absorption of the mercury ions by the precipitates

A large number of mercury compounds are used externally for their antiseptic and germicidal properties

Heart The inorganic salts and so also the organic compounds such as mercurochrome rapidly produce cardiac irregularities and fibrillation The response of the isolated heart to the action of mercury varies in different animals The frog's heart is very resistant to the action of mercury and a concentration as high as 1 in 50 000 is necessary to show any marked effect The turtle's heart ... 000 In all cases mercury produces depres ... rk has however shown that the mercury ... stimulant action on animal tissues A 1 in ... to the perfusate distinctly stimulated the ... orce of contractions

Gastro intestinal tract M ...

al

... blood and

Mercury has very little action on the ferments of digestion The antiseptic action on the intestine especially of calomel is due to retardation of putrefaction and decomposition of foodstuffs by increased peristalsis that hurries the contents down the intestinal canal

Kidney The kidneys are stimulated with small doses and diuresis is produced The ... mild renal irritation ... ion in the ... in a few ... he tubules. ... nt features

Central nervous system The action on the central nervous system is not marked in therapeutic doses Tremors and giddiness may be temporarily produced Workers in mercury mines in mirror works, barometer and thermometer factories are specially liable to develop

but they are extremely rare

Metabolism The effects of mercury on metabolism are not fully understood, but in general resemble those of arsenic and phosphorus Small doses are said to improve the nutrition and lead to acceleration of metabolism of proteins Prolonged administration may give rise to cachexia

Fate in the body Metallic mercury and mercury compounds are readily absorbed from all surfaces including the intact skin Complex chemical changes are said to occur in the course of absorption The absorbed mercury remains in the blood only for a short time but may remain in the tissues for a very long period and continue to exert its specific action by slow ionization and reabsorption

Excretion The excretic
Traces are also found in th
in which it is excreted in t
therapeutic doses excret on
tration ceases In the case (
depots are maintained and traces may be excreted intermittently for as long as six months or even longer A considerable portion of the absorbed mercury however is retained indefinitely in the tissues

The fate of absorbed mercury and its distribution in the body tissues is not fully known Its concentration in the blood as has already been pointed out declines rapidly and only

spleen, brains and lungs come next in order The fat and the muscles contain a low concentration but the quantity as a whole in the latter is fairly high Mercury is found in the bones In the body fluids and in the amniotic fluid mercury is found in fairly good concentrations It passes through the placental circulation and hence it is claimed that congenital syphilis may be treated by mercurial inunction of the mother Mercury in the spinal fluid increases in direct proportion to the number of doses and the amount of the drug administered.

Is antiseptic

Mercury compounds were probably among the earliest antiseptics used but it has now been recognized that their germicidal activity is not as potent as was supposed The action is dependent on Hg ion which combines with all proteins there being no selective action on the bacterial protoplasm The inorganic salts of mercury have an irritant action and poor penetrability They are fixed by proteins and lose their activity and are toxic It has also been shown that their action is reversible as removal of mercury by precipitation from a supposedly sterile solution results bacterial growth Spores are also very resistant to the action of inorganic compounds

On account of these disadvantages a number of organic compounds of mercury were synthesized.

Mercury compounds

(1) *Soluble* —Perchloride of mercury (corrosive sublimate) is sold in tablets containing 0 125 and 0.5 gm It is used in dilutions of 1 in 1 000 for sterilizing clothes and 1 in 2 000 for sterilizing surgeons' hands Other compounds are cyanide benzoate salicylate and succinamide of mercury and red mercuric iodide

(2) *Insoluble*—Such as yellow mercuric oxide, calomel

(3) *Complex organic combinations*, such as mercurochrome, metaphen, merthiolate, mersalyl, etc.

(2) Therapeutic uses of Mercury

As cathartic and intestinal antiseptic Perchloride of mercury is seldom used internally as it is a strong irritant and corrosive and may give rise to toxic symptoms if the dosage is not properly controlled In small doses however it is still used by clinicians for its antiseptic and astringent effects on the gastro intestinal tract Insoluble mercury salts are preferred for this purpose Calomel dissolves so slowly and to so limited a degree that the intestinal irritation and toxic symptoms commonly produced by the soluble compounds are not manifested at all On the other hand a very mild irritation is produced which stimulates both the large and the small intestines and increases their peristaltic movements resulting in catharsis Ordinarily calomel produces dark green semisolid stools in ten to twelve hours The green colour is due to biliverdin The appearance of biliverdin in the stools has been considered to be due to the effect of calomel causing an increased flow of bile This however is an erroneous idea Numerous investigations with biliary fistulæ have shown that calomel does not increase the flow of bile

Calomel is commonly used in therapeutics for its antiseptic action and it is *one of the most useful and efficient antiseptics known* The antiseptic action is said to be due to the slow formation of mercuric chloride from calomel in the al ka [illegible] owing the administration of calomel th [illegible] this is reflected in the decrease of the [illegible] l may favour bacterial growth by diminishing intestinal resistance

[illegible] *to 5 gr or more commonly* are given The method of view of the fact that this method ensures better solution and consequently more efficient action Grey powder (hydrarg cum creta) is specially suited for children The mercurials are of value in obstinate constipation attended with biliousness and they can be conveniently administered at night followed by a saline purgative in the morning

Calomel should not be used continuously for a long time on account of its systemic actions This is ordinarily unimportant because any excess is generally excreted before it is absorbed But [illegible] irritations ulcerations may favour r [illegible] therefore always advisable to follow [illegible]

(i) Mercury in syphilis

Mercury has been in use in the treatment of syphilis from the 15th century and was the only drug having a definite anti syphilitic action till the arsenicals came into use in the early part of 20th century After the introduction of bismuth compounds it fell into background and now only used rarely The reason for this is that mercury has a low therapeutic index against syphilis *Besides* this its action is very slow and treponemes persist in the lesions because of delayed healing It is doubtful if it has ever cured this disease during the centuries it has been in use *What it probably does is that* because of its treponemostatic action it reduces the infection to such a low level as to enable the body defences to cope with the infecting spironemes

Mercury is undoubtedly inferior to arsenicals and bismuth compounds and even as an adjuvant to arsenicals it is much inferior to bismuth in as much as it gives a higher incidence of relapses and allows a lower number of serological

reversals By itself it does not prevent the infectiousness of the disease nor does it stop its progress At the same time it is more toxic than bismuth and has a lower therapeutic index Bismuth should therefore be used when arsenicals are contraindicated and mercury should only be used under very special circumstances in early syphilis

Mode of action of mercury in syphilis The mechanism of antisyphilitic action produced by mercury is not understood Though the metal has direct lethal effects on the treponema the concentration necessary to produce such lethal effects is never reached in the blood in doses which do not exceed the tolerance of the patients

Mode of action of mercury in syphilis

(ii) Prophylactic uses

Mercury was used as a prophylactic remedy in syphilis for a long time It often prevents the onset of primary and secondary lesions if applied locally before the treponema have penetrated *i e* within 4 or at the most 8 hours after exposure It has no preventive action 12 hours after exposure The usual procedure recommended is to cleanse the site of the suspected infection with soap and dress the part with an ointment containing 33 per cent of calomel or 0 3 per cent of corrosive sublimate (Neisser Seibert ointment) The prophylactics containing mercury do no real good but may do harm by preventing the recognition of infection

Mercury still occupies an important position in the prophylaxis of syphilis the preparation used being calomel ointment Used properly within an hour after exposure it is said to prevent infection in 99 per cent of cases Mercury ointments used are —

U S army—Mercurous chloride 30 per cent benzoated lard 65 per cent white wax 5 per cent *U S Navy* Mercurous chloride 33 per cent Camphor 2 per cent phenol 30 per cent anhydrous lanoline 39 per cent benzoated lard 20 per cent bees wax 3 per cent Prophylaxis also includes intra urethral injections of argyrol 10 per cent or protargol 2 per cent solution by way of combined prophylaxis against syphilis and gonorrhœa

As a diuretic All mercury compounds during their excretion stimulate the renal epithelium and produce a distinct diuretic effect This diuretic effect is particularly marked when there is œdema of the tissues This property of mercury was known long ago and clinically made use of in the form of Guy s pill which is a combination of blue pill (pilula hydrargyri) with digitalis and squill The diuretic effect of calomel was however unreliable and the diarrhœa set up during its administration was a very objectionable feature to the patients Within recent years a number of stable organic me[illegible]
(see detailed descri[illegible]
irritant and non tox[illegible]
and intravenously
well known members of this group

[illegible]

[illegible] days These preparations have also been used in œdema following anæmia and hookworm disease In the endemic ascites of the tropics met with in Bengal and Bihar novasurol and salyrgan have given good results.

Skin diseases Mercury has been applied externally in various skin diseases of parasitic origin such as itch ulcers condylomata and ulcers of syphilitic origin. In all these conditions mercury acts as a disinfectant and irritant Ointments containing mercury in metallic form such as unguentum hydrargyri are the least irritant of all Mercury oleate, yellow oxide red oxide and ammoniated mercury are also commonly used As a lotion black wash or yellow wash is the common external application, as a dusting powder calomel may be used on ulcerating surfaces *e g*, in corneal ulcers

Gonorrhoea and gleet Mercury has been used as a lavage in urethritis a lotion of 1 in 4 000 to 1 in 2 000 of mercuric chloride being commonly employed

(3) Modes of Administration

Mercury is administered chiefly by (1) inunction (2) oral route (3) intra muscular injection and (4) intravenous injection

Inunction Mercury when triturated with fat forms a colloidal suspension which is absorbed when rubbed on the skin Histological examination of the skin after inunction with mercury shows that the mercury globules do not enter the epidermis but that they penetrate deep into the sweat glands and hair follicles and from there they are absorbed It is a fairly effective method of administering mercury Undesirable local and gastro intestinal effects are not noticed and it is easy to avoid serious overdosage The disadvantages are that it is time consuming and disagreeable and the exact amount absorbed cannot be accurately determined

For this purpose a strong mercurial ointment containing 50 per cent of metallic mercury is used but if it is irritating it may be diluted to 25 per cent with cold cream The daily dose is 4 0 gm Full instructions should be given to the patient how to use it *i e*, where and how to rub it in Inunctions should be discontinued if teeth start aching, generally there are no cumulative toxic effects Various areas of skin should be used by rotation as rubbing has to be continued for 6 to 10 weeks every night in the intervals between courses of arsenicals Inunction is not used now

Oral administration The oral route is the easiest method of administering drugs but it is not suitable in the case of mercury and has now been largely replaced by other methods in adults In the case of children this method is still retained for the sake of convenience Considerable quantities of mercury can be absorbed from the gastro intestinal tract even when the insoluble mercurous compounds are administered This is proved by the incidence of salivation and the urinary excretion which is quite as high as with inunctions and intramuscular injections The gastro intestinal irritation is the serious drawback which has restricted oral administration The patient also cannot be kept under control and the rate of absorption cannot be determined with any degree of accuracy

Mercury can be given orally either as a solution of a soluble mercury salt or as a pill containing an insoluble mercurous salt or as metallic mercury The usual preparations used in order
(Proto iodide) dose 0 01 to 0 05
0 05 to 0 2 gm (1 to 3 gr)
Hydrargyrum chloridum corrosiv
prevent local corrosion mercuric chloride is administered with excess of potass u iodide or in milk

Rectal administration fumigation inhalation of mercury vapourized at room temperature are no longer used in practice

Intramuscular injections Three classes of preparation are used for intramuscular injections (1) water soluble ionizable compounds (2) water soluble non ionizable compounds and (3) water insoluble compounds

Water soluble ionizable compounds Mercuric chloride (1 ccm of 1 per cent solution) injections are very painful and should not be used because pain and sloughing of tissues may follow though some salts like the benzoate succinimide, cyanide biniodide (double salts) cause comparatively less pain than mercuric chloride in doses of 1 0 gm

Basic mercuric salicylate is insoluble in water but is soluble in sodium chloride solutions or alkalis *It is given suspended in oil* but is absorbed as *rapidly* as the water soluble salts It causes very little pain

Water soluble non ionizing compounds These include novasurol salyrgan and mercurosol The antisyphilitic action of the first two is practically negligible They cause very little local irritation and are not toxic in therapeutic dosage The absorption is very rapid and fairly complete These are used as diuretics and will be referred to again

solution ccm weekly Absorption is uncontrollable and toxic effects are common

Intravenous injections Intravenous injections of mercury were introduced with the idea of securing a maximal concentration of mercury in the blood without any of its unpleasant and untoward local actions These however did not attain any degree of popularity Preparations for intravenous injections are

(1) *Ionizable salts* Mercuric chloride oxycyanide benzoate and the double iodide have been administered in 1 per cent solution in doses of 1 to 3 ccm daily or every second day

(2) *Organic compounds* Novasurol, salyrgan mercurosol have been used to a much greater extent than the ionizable mercury salts As has been already stated these compounds are not very effective in syphilis and their chief use is in connection with the production of diuresis With these compounds as with *ionizable salts urinary excretion of the metal proceeds at a rapid rate within* an hour or two and declines promptly reaching an insignificant level within 8 hours after injection These therefore suffer from the same disqualification as the other group Moreover novasurol and mercurosol produce diarrhœa and dysentery like symptoms in some patients Salyrgan is not reported to have caused any untoward symptoms

Disadvantages of intravenous administration It will be seen that intra venous administration of mercury is not as effective therapeutically as the intra muscular method Most of the compounds irritate the veins at the site of injection and tend to produce fibrosis and occlusion of the vein They also present danger of embolism and colloido clastic shock Urinary excretion studies indicate that the high concentration reached by intravenous injection is of too brief a duration to be useful in chemotherapy and the maintained level is generally too low, even with daily injections

(4) Toxic Effects

Acute t–

poisoning
coagulation
and discolor
features A

are also met with Twenty four hours later mercurial *stomatitis develops but* this is not very severe Later the large intestine and kidneys become involved The urine becomes scanty and highly coloured with copious albumin and casts Anuria has occurred in some cases followed by death within a week If the nephritis is not fatal a membranous colitis develops with ulceration and hæmorrhage Hepatic degeneration may supervene Death occurs from circulatory failure in some cases

Post mortem examination shows the mucous membranes of the mouth pharynx glottis œsophagus and stomach to be corroded and extremely congested In the colon necrosis and ulceration and consequent congestion are met with The kidneys show signs of acute nephritis and the liver cells are degenerated in some cases

The symptoms of acute mercurial poisoning are not produced by therapeutic doses of the drug and are therefore not very important from the clinical stand point A sort of subacute mercurial poisoning is the usual outcome of prolonged treatment The symptoms which have to be guarded against by the physician in such cases are of a milder nature and consist of localised chronic inflammations especially stomatitis colitis nephritis etc The stomach and large intestines are usually not involved as in the case of acute poisoning

Stomatitis is usually the earliest symptom of subacute and chronic mercurial poisoning It occurs constantly by whichever route mercury is administered A metallic taste in the mouth soreness of the gums and salivation are the primary *manifestations If not noticed in time and if the drug is pushed further blacken*ing of the gum margins loosening of the teeth uncontrollable salivation and later fatal ulceration of the mouth may supervene The kidneys are specially susceptible to mercury and therefore albuminuria is a common finding The damage however is not as marked as in cases of acute poisoning and tends to involve the interstitial cells more than the glomeruli Long continued exposure to relatively small doses leads to a slow and insidious development of chronic poisoning usually with some stomatitis and renal irritation but with additional nervous and nutritional disturbances Cachexia with anæmia and malnutrition are found together with psychic irritability tremors and restlessness

Treatment of mercurial poisoning The prognosis in cases of acute mercurial poisoning is grave unless prompt emesis is resorted to within 15 minutes of the administration of the poison Mercury is rapidly fixed in the mucous membrane of the stomach and once it gets fixed the antidotes (milk, calcium sulphide, thiosulphate etc) naturally cease to react Lavage is sometimes helpful by removing the mercury which may remain free in the stomach at the time The simplest antidote consists of three raw eggs in a quart of milk followed by gastric lavage. *The local antidotes must be followed by an emetic* to expel any poison which might remain unabsorbed Administration of glucose and alkalies is *useful and hot packs in the kidney region may help in soothing the* renal irritation Sodium thiosulphate has been advocated intravenously but is not very satisfactory

In subacute cases stomatitis and colitis are the symptoms to be attended to Stomatitis is most effectively prevented and treated by hygiene and care of the teeth Septic conditions about the gums are especially liable to cause poisoning and should be attended to before mercury treatment is started When stomatitis is very severe mercury should be stopped and mouth washes and gargles of an antiseptic nature should be prescribed Hydrogen peroxide potassium chlorate *potassium* permanganate are all useful and should be used several times a day The gastro intestinal troubles usually yield to sedatives such as chalk and bismuth Stimulants whenever necessary should be given

Cases of chronic mercurial poisoning seen in workers in mercurial mines etc., cannot be much improved even with vigorous treatment In these cases, prevention and protection against unnecessary exposure are more important

(5) Preparations of Mercury

The preparations of mercury which are recognised in the British Pharmacopœia are too well known to require any detailed description In recent years attempts have been made to improve mercurial therapy and a number of organic compounds have been prepared

[illegible] oxy mercury fluorescein [illegible] It is given intravenously [illegible] solutions of 1.0 per cent [illegible] desirable Mercurochrome [illegible] travenous use are on the market

Pharmacological action Mercurochrome is said to have a disinfectant action and is employed as a general antiseptic in surgery A 2.5 per cent solution is useful for surface lesions for painting on the mucous membranes or for injection into sinuses Given intra [illegible] ent solution [illegible] of 0.2 mgm [illegible] are therefore [illegible] ent solution [illegible] the bile and [illegible]

Pharmacological action

Therapeutic uses Mercurochrome is recommended in all forms of bacterial diseases It has been used in gonorrhœa gonorrhœal arthritis cystitis and pyelitis As a vesical antiseptic 1 per cent solution can be used for lavage without causing any pain The routine method of giving vesical injections is to give 30 ccm of a 1 per cent solution *stronger solutions should be used with great caution A 5 per cent solution is used as a* uretheral lavage Gonorrhœal arthritis is said to be favourable influenced by intravenous medication [illegible] in plague [illegible] affections [illegible] in 1 to 5 gr [illegible] 3 weeks It is usually given in keratin-coated capsules and no harmful or distressing effects have been observed Stools changes into a deep mahogany colour and must be kept thus so long as the drug is administered Rarely the drug produces intestinal cramps and nausea

Therapeutic uses.

Mercurochrome has also been used in the form of colonic irrigations a 5 per cent solution being injected slowly into the rectum in amœbic dysentery In ulcerative colitis lavage with 6 to 8 ounces of a 0.3 per cent solution has given good results It has been used against leprosy for checking rapid retrogression in the treatment of ulcers following on disintegrating tubercles and in healing neurotropic ulcers weekly injections of 1.0 per cent solutions are generally given combined with chaulmoogra oil esters

Toxic effects The toxicity of different samples varies Salivation stomatitis and severe diarrhœa commonly nausea and vomiting rose coloured stools rigors and rise of temperature may occur after large doses The kidneys may be irritated and albumin may occur in the urine. The margin between the therapeutic and toxic doses of mercurochrome is variable and small As a rule no gastro-intestinal disturbances are produced till the drug has been continued for a week

Toxic effects

Flumerin Flumerin is the disodium hydroxy mercuri fluorescein It is a red odourless *powder somewhat hygroscopic containing 33 per cent of mercury It is soluble in hot* water about 1 in 10, but insoluble in alcohol ether or chloroform

Novasurol Novasurol is also known as merbaphen it is the double salt of sodium mercuri chlorphenyl oxyacetate with diethyl barbituric acid (barbital) Novasurol occurs as a white crystalline powder soluble in cold water and contains about 34 per cent of mercury It was originally intended to be an antisyphilitic remedy but has come to be used as a diuretic When given intramuscularly it is excreted in the gut and doses higher than 2 ccm are liable to cause gastro-intestinal irritation with profuse watery stools

The action of novasurol on the kidneys is important since it has been used in cases of nephritis with œdema The beneficial effect is more marked in œdema due to myocardial insufficiency than in cases of nephritis where it is contraindicated The exact mode in

which novasurol brings about diuresis is not known In man toxic symptoms have occurred after novasurol In mild cases certain disagreeable symptoms such as headache vertigo nausea vomiting stomatitis diarrhœa fever and rash are seen These symptoms are generally mild and clear up with the discontinuance of the drug In certain cases hæmaturia has occurred, death from the effect of novasurol is also on record

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nt solution is advised with
he diuresis

Salyrgan This is another member of the organic mercury compounds which has been used in recent years very extensively in cardiac or renal œdema to produce diuresis It is a complex synthetic mercurial prepared by the action of mercury acetate and methyl alcohol on sal cyl allyl amido-acetic acid and subsequent conversion to the sodium salt. The mercury content is about 40 per cent in non ionizable form It is a white crystall ne powder soluble 1 in 1 of water It has been demonstrated to have spirochæticidal properties The diuretic property of the drug is well known

Metaphen It conta ns abo t 58 to 60 per cent of mercury Metaphen is a yellow substance insolubl
of 1 in 5 000 to 1
solutions of 1 in
solutions of 1 in

9. Iodides in Syphilis

For many years mercury and iodides were the only drugs available in the treatment of syphilis The iodides have no direct destructive action on the spirochaetes They however have a definite action on the granulomatous tissue such as is found in leprosy actinomycosis etc and in some obscure way they act on the syphilitic lesions According to some authorities they help the action of arsenic bismuth and mercury probably by increasing their penetrability into the syphilitic tissues in a way not yet understood It is doubtful if iodides occur in such tissue in a higher concentration than plasma They act on the syphilitic tissue even if they are not combined with other antisyphilitic drugs (arsenicals etc) They are said to inhibit the action of an antiferment and in this way the proteolytic enzyme is enabled to dissolve the necrotic tissue

In early lesions iodides appear to have no marked action and arsenicals and bismuth compounds can produce their effects without their intervention In late syphilis it is believed that if used in combination the lesions are healed more expeditiously They are particularly effective in gummatous lesions cardio vascular syphilis syphilis of bones skin and meninges In meningitis there is definitely an improvement in the symptoms They should be given in large doses in all forms of gummatous lesions in combination with arsenic and bismuth Iodides of sodium and potassium are effective the other iodides having no particular advantages They can be given in ordinary mixture with syrup or in milk to disguise their bitterish taste In acute conditions such as meningitis as much as 15 to 20 grains have to be given three times a day if the patient can tolerate such doses Formerly iodides were always combined with mercury but this is not the practice now and antisyphilitic treatment is given separately In granulomatous conditions even larger doses are given The drugs are best given by the mouth and before meals, they should be given with plenty of fluid

Absorption and excretions —Iodides are readily absorbed from the mucous membrane They are absorbed from the stomach and are widely distributed throughout the tissues and body fluids in the same way as chlorides and bromides They penetrate the red corpuscles but otherwise mostly remain extracellular in the body fluids The view was formerly held that they are taken up selectively by the pathological tissues (granulation tubercular etc) They are completely excreted from the body in 24 hours the excretion of the iodine ion is hastened by administration of large doses of chlorides Iodides occur as HI in gastric juice saliva milk bile sweat effusions etc

Mode of action —The iodine ions appear to have no specific action on any tissue in the body, nor even on the nervous tissues Their action in syphilitic diseased tissues and in inflamatory conditions is not understood It is well known that in tuberculous conditions they are contraindicated because they irritate and even lighten up dormant foci Their action on gummata is probably of this nature which leads to their resolution

Toxic effects —Acute poisoning is not common unless the patient has idiosyncrasy (sensitiveness) for the drug Before giving iodides by the intravenous route the sensitivity should be tested The chief danger is œdema of the larynx and consequent suffocation and rarely multiple hæmorrhages in the skin and mucous membranes

Iodism is the name given to chronic poisoning and this may suddenly develop when iodides are being taken Individuals however vary in the degree of their sensitivity Sometime iodism is produced when small doses are given and disappears with larger doses but it generally comes on when dosage is on the high side There is a peculiar metallic taste in the mouth burning sensation in the throat soreness in gums and teeth salivation coryza sneezing irritation of the eyes heaviness in the head or headache in fact the symptoms resemble a cold in the head There is increased secretion from the bronchii which in severe cases may lead to œdema of the lungs Skin eruptions occur after prolonged use Mental depression and occasionally severe diarrhœa and cachexia ensue

Treatment —In acute poisoning gastric lavage with starch solution or sodium thiosulphate solution (5 per cent) may be used to remove iodine Normal saline is given intravenously Iodism generally disappears a few days after the drug is stopped, excretion is hastened if large amounts of fluid and sodium chloride are given

Preparations —" [illegible] *solution* which contains 5 pe [illegible] im iodide is used A saturate [illegible] ccm A number of organic [illegible] have been introduced which are less irritating but slower in action Some of these Iodulbin (21 5 per cent iodine in blood albumin) Iodocasein (18 per cent iodine) are given in doses of 0 3 to 0 5 gm

Lipiodol is a 40 per cent solution in poppy seed oil dose 1 0 to 2 5 gm daily It is introduced into the bronchi for taking X ray pictures *Riodine* is a 17 per cent solution in castor oil *Diodrast* a water soluble organic compound containing 49 8 per cent of iodine is used intravenously for taking X ray pictures of the urinary tract

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PART IV

REMEDIES USED AGAINST BACTERIAL DISEASES

CHAPTER I

BACTERIAL DISEASES—SERA & VACCINES

GENERAL CONSIDERATION BACTERIAL ORGANISMS PATHOGENICITY OF ORGANISMS RESISTANCE OF THE BODY AGAINST BACTERIAL INFECTION (IMMUNITY) MICROBIAL ANTAGONISM AND ITS BIOLOGICAL UTILIZATION—SPECIFIC IMMUNE THERAPY IN BACTERIAL AND VIRUS DISEASES—VACCINE THERAPY PREPARATION OF VACCINES VARIETIES OF VACCINES METHODS OF ADMINISTRATION THERAPEUTIC USES—SERUM THERAPY MODES OF ADMINISTRATION REACTIONS FOLLOWING ADMINISTRATION OF SERUM ANTITOXIC AND ANTIBACTERIAL SERA ANTIVIRAL SERA—BACTERIOPHAGE THERAPY NATURE OF BACTERIOPHAGE PREPARATION OF BACTERIOPHAGE ROLE OF BACTERIOPHAGE BACTERIOPHAGE IN PROPHYLAXIS AND TREATMENT OF DISEASE.

1. General Consideration

(1) Bacterial organisms

Bacteria are minute unicellular masses of protoplasm which are devoid of chlorophyll and definite nuclei The dimensions of most of the cultivable forms of bacteria are of the order of low multiples or submultiples of a micron (μ) measuring 1/25 000 of an inch These bacterial cells may be coccal or spheroidal bacillary or cylindrical or spirillar in shape Many bacilli and most spirilla and vibrios are more or less actively motile by means of flagella The most common method of multiplication of bacteria is by simple binary fission each cell dividing into two daughter cells by constriction these daughter cells again undergo similar division and so on Throughout Nature bacteria are widely distributed However among the innumerable varieties of bacteria present in Nature there is a very limited group which is capable of becoming parasitic upon the bodies of higher animals and among these a still smaller proportion which is capable of being 'pathogenic' *i e* producing disease The exposed parts of our bodies the mucous membranes of the nose the conjunctivae and the intestinal and respiratory tracts are constantly inhabited by a rich bacterial flora Many of these consist of ordinarily harmless bacteria (saprophytes) and some are definitely beneficial and even essential for life

The mere presence of any *pathogenic organism in or on the body does not* necessarily give rise to clinical disease For the clinical manifestation of the disease to be produced it is essential that in addition to gaining access to the tissues the organism should be capable of maintaining itself and of multiplying in the tissues to a lesser or greater degree There is a regular struggle between the invading organism and the defensive forces of the host If the pathogenic organism gains a foothold in the body of the host the infection is established and it is balance between the two opposing forces which decides the ultimate outcome of recovery or death Before taking into consideration the diseases produced by the pathogenic bacteria it is therefore desirable to refer briefly to these two opposing forces the capacity of the organism to cause infection *i e*, its pathogenicity and the resistance of the body against bacterial infection

(2) Pathogenicity of organisms

After an organism has gained a foot hold in the body of the host its virulence or pathogenicity depends on its toxigenic or invasive powers or on a combination of both these properties Some organisms such as the *C diphtheriae* and *Cl tetani* produce their effects by the local production of a powerful toxin which diffuses into the tissues and produces its effects on cells which are far removed from its site of production Others such as *B anthracis* and *Past pestis* produce their pathogenic effects mainly by their power to invade the tissues and their main pathological effects are produced at the site or sites at which they are multiplying Other organisms such as *Str pyogenes* are both toxigenic and invasive

Bacterial to

Bacterial toxins The harmful effects of bacteria are dependent on the toxins they produce and on the constituents or products of bacterial cells such as coagulases fibrinolysins substances increasing the permeability etc which though not directly toxic, influence the course of bacterial infection The toxins produced by the bacteria include filterable exotoxins which diffuse freely from site of infection and act specifically on certain sensitive cells hæmolysins and leucocidins which act directly on red blood cells leucocytes and endotoxins which are contained in the bacterial cell and are liberated only when the cell disintegrates

Relationship between virulence and dosage—There is an inverse relationship between the virulence of the organism and the numbers or dosage which can bring about infection In case of highly virulent organisms such as the anthrax bacillus the inoculation of a very small number of bacteria may suffice to initiate infection It has been shown experimentally that a single anthrax bacillus may cause fatal infection in about 28 per cent of mice while ten anthrax bacilli are capable of destroying all the infected mice In contrast to this high virulence is the relatively low virulence of freshly isolated strains of meningococci or typhoid bacilli for mice It appears to be quite reasonable to suppose that under natural conditions the spread of infectious diseases is conditioned to a great extent by the dose of the infecting agent We can imagine that in highly infectious diseases such as measles the amount of infecting material required to produce the disease is small while in diseases like whooping cough which are less readily contracted a greater amount of inoculum is required

The virulence of an organism is subject to great variations It may be quite easily lost for example by growing the bacteria on artificial media in the laboratory Indeed decrease in pathogenicity is almost the rule with most bacteria kept in the laboratory on ordinary artificial media The virulence of such organisms may be restored by passage through an appropriate animal By this way one can also frequently enhance the virulence of an organism for a species of host to which it is not naturally adapted Variations in the virulence of the organisms may be of importance in deciding the characteristics of the various epidemics

Channel of infection—The path of entrance of an infecting organism is quite as important as its virulence Even when an organism is pathogenic for the given animal is virulent and enters in adequate amounts it may not produce the disease unless it enters the body by the particular path to which it has become pathogenically adapted Thus inoculation of the skin with virulent streptococci will cause progressive infection but similar inoculation with the typhoid bacillus or the cholera vibrio will have no such effect On the other hand while the swallowing of the typhoid bacillus will usually result in typical infection swallow

ing of pyogenic cocci will usually have no effect Similarly the virus of swine influenza produces the typical disease in swine only when inoculated by the intranasal route

(3) Resistence of the body against bacterial infection

So far we have discussed only the pathogenic powers of bacteria The resistance of the host is the other factor to be considered as every infectious disease is the result of the struggle between these two opposing forces Thus a micro organism may be able to cause fatal infection in one individual but may be only slightly virulent or even quite harmless for another Conversely an individual may be highly susceptible to one micro organism but resistant to others Even the reactions of an individual to one and the same organism may differ at different times and under different circumstances

Immunity The resistance or 'immunity of the host is of different kinds and of different degrees The immunity may be innate or genetic or it may be acquired Different species of animals are known to display varying degrees of innate or genetic (as opposed to acquired) resistance to the different pathogenic organisms The acquired immunity is the result of natural infection or artificial immunisation When acquired immunity follows infection or inoculation with vaccines or toxins of the pathogenic agent it is known as active immunity as the tissues of the infected or injected individual play an important part in bringing about the increased resistance When acquired immunity is the result of transference of blood or serum of an actively immunised animal it is known as 'passive immunity since the tissues of the recipient play a relatively passive part Topley and Wilson summarise this classification of immunity in the following table —

1 Innate or genetic immunity
2 Acquired immunity
   (a) Active
      i Naturally acquired
      ii Artificially induced
   (b) Passive
      i Naturally acquired
      ii Artificially induced

Genetic and passive immunity —About the innate or genetic immunity one

passively acquired immunity is the result of transference of ready protective substances contained in the blood or serum of actively immunised animals These substances may be transmitted naturally from the mother to her young either by the placental circulation or in the colostrum Artificial passive immunity consists in injecting the serum of actively immunised individuals or animals The passive immunity is always short lived

Active acquired immunity The actively acquired immunity is the result of protective substances being formed by the tissues of the infected or injected individual Active immunity is always of a longer duration than the passive and in case of certain diseases such as measles small pox, etc the immunity may last for life The protective substance or substances concerned in a specific

bacterial immunity are the antibodies which are prepared by the tissues of host in response to the stimulation produced by the 'antigens of the particular micro organism We now know that the essential agents in effective antibacterial immunity are those antibodies which act on the surface antigens of smooth, virulent bacilli

Role of recticulo endothelial system in immunity The cells of the recticulo-endothelial system of the body play an essential part in the production of these antibodies It will be remembered that these are the very cells which are responsible for removal of bacteria and particles of inert material from the blood The recticulo endothelial system includes a wide range of cellular elements which have a wide distribution in the body but all these cells function in the same manner like a single physiological unit The spleen is the biggest of the single depot of these cells the rest of the cells of this system are found in bone-marrow liver, lymph glands and connective tissues

Role of recti endothelial ... imm

Now we may refer briefly to the role of these antibodies in the antitoxic and the antibacterial immunity The protection afforded by the anti toxic sera depends almost entirely on the interception and neutralisation of the toxin before it reaches the susceptible cells Once the toxin has reached the susceptible cells the anti toxin is relatively ineffective The neutralisation of the toxin by anti toxin can be seen both in vitro and in vivo The anti bacterial immunity depends on increasing the efficiency of the clearing mechanism present in a normal individual As a result the immunised animal deals with the virulent strain of an ... eals with an avirulent or slightly ... this is specific i e, this increase ... nto play only for the particular

Non specific factors Non specific factors occur in connection with body resistance We have considered so far the specific resistance of the body to individual organisms There is good ground for belief that any agency which interferes with the general health of the patient or which damages the tissues of the host will diminish natural or acquired resistance Thus fatigue and chronic alcoholism cause a general deterioration of health ... vitamins e... injudicious ... the suscepti... the tissues and creates a nidus for the growth and multiplication of the invading organisms, fluctuations in temperature and humidity affect the local condition in the upper respiratory and the gastro-duodenal tracts and may lower the local ... course of infectious diseases ... hat seasonal variation affects ... the parasite

Non spe factors

Local Immunity The mechanism of ... above depends on the p... the pathogenic bacteria ... the toxin and prepares ... antibodies are distribute... generalised one There ... that under certain circumstances immunity localised in certain areas of the body may exist in the absence of a general immunity The work on experimental erysipelas in rabbits has shown that following intracutaneous injection with living streptococci local

areas of skin may be more resistant than the general skin to further intracutaneous injections of these organisms It has been found that after repeated inoculations there is generalised skin immunity and that this is associated with appearance of specific antibodies in the blood

This local increase in resistance has not been found to be of specific nature and local non specific inflamatory reactions following injection of substances like *mustard oil and sterile broth etc are capable of producing* non specific local immunity Histological studies show that this non specific increase in local resistance is determined to a great extent by mobilisation of various phagocytic cells Thus there *is no doubt that local immunity as opposed to general immunity* does exist but the increased local resistance is largely determined by non specific factors although the possibility of specific factors being involved can not be excluded

nity

Tissue immunity—The problem of the existence of local immunity as opposed to general immunity is quite distinct from although it is often confused with the problem of the existence of tissue or cellular immunity as opposed to humoral immunity The propounders of the theory of tissue immunity believe that local tissue immunity as such and independently of associated humoral immunity confers general immunity on the animal Besredka *(1919 1920 1921)* has been the chief exponent of this view Starting with the observations regarding the specific localisation of many pathogenic bacteria in particular tissues of the body *Besredka reasoned that these particular tissues are the only tissues* susceptible to the particular organism and that if these tissues are immunised the whole individual will be immunised According to this theory it is only *the cells in the skin that are susceptible to anthrax bacillus* and only the cells in the intestine that are susceptible to typhoid para typhoid and dysentery bacilli The immunity to infection of an immunised animal according to his theory

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ies

results since the organism is rapidly destroyed by the phagocyt[illegible] this theory immunisation would consist in rendering the receptive cells resistant by desensitizing them with products derived from the particular bacteria The experimental evidence on which Besredka based his theory has been challenged His statement that after oral administration of dysentery or typhoid bacilli the [illegible] may appear in the blood of rabbits after *the first administration but*

a culture of anthrax bacillus was much less [illegible]
intracutaneously Cultures of anthrax bacillus in candles sealed in the peritoneal cavities of nine rabbits produced death in seven after intervals varying from 6 to 51 days Burke and Barnes (1931) succeeded in producing initial anthrax infection in the subcutaneous tissue they utilised the bactericidal action of gentian violet to make sure that the skin was not infected at the time of the subcutaneous injection

[illegible] of this theory to
[illegible]nd vaccine
[illegible]n by local

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application of dressings saturated with filtrates of cultures of these organisms There is evidence that the oral administration c
immunising value, and we know that oral
bacteria is often followed by passage of ant
intestines, and by the consequent production of
tion of vaccines is a less reliable and quantitatively very uncontrollable substitute for subcutaneous injection Regarding the local application of the so called 'anti virus' preparations in the treatment of staphylococcal and streptococcal skin condition it would appear that the result is entirely non specific since infiltraton of the skin even with sterile broth raises the local resistance

(4) Microbial antagonism and its biological utilization

Bacteria causing cholera dysentery, typhoid, etc enter the soil but do not survive there for long It was suggested that the cause of this disappearance is to be looked for among the soil inhabiting microbes antagonistic to the pathogens Harvey induced a typhoid carrier to urinate on soil and fowels After 30 hours the organism could not be recovered from the soil that was still moist
to dry Rhines showed
n non sterile soil it was
produce substances that
it their destruction

The antagonist organisms described so far can be divided into four groups The first group comprises various strains of *Ps aeruginosa* and *Ps fluorescens* The active substance according to Hettche is of a lipoid nature, various workers have reported it to be active on certain gram positive and gram negative organisms

The second group comprises various spore bearing bacteria of *B mycoides* and *B mesentericus* group These bring about lysis of diphtheria, typhoid and cholera organisms They
'Gramicidin' from a soil b
large numbers of virulent
administered to mice sever
results have also been obtai ... in treating bovine mastitis with this substance.
Waksman
and he growth
of *S*

The fourth group consists of antibiotics derived from fungi *e g* penicillin

The utilization of the antagonistic activity of various soil microbes opens a new field for the preparation of various chemotherapeutic agents for combating human animal and plant diseases, and the extraction of these antibacterial or anti toxic principles, and determining their nature and mechanism of their action can lead to the development of chemotherapy on a rational basis

2. Specific Immune Therapy in Bacterial and Virus Diseases

In the prophylaxis and treatment of a large number of bacterial and virus diseases specific immune therapy has been employed With the introduction of sulphonamides and antibiotics the use of sera and vaccines in the treatment of many infectious diseases has become of secondary importance Both these groups of therapeutic agents have powerful bacteriostatic and bactericidal properties They do not, however, neutralise the toxins produced by the infecting organisms Sera are, therefore, used in combination with them whenever it is desired to

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or 'receptive cells with which it ...

activity of the phagocytes If it reaches the body through some other route which avoids contact with the skin, no receptive' cells are encountered and no disease results since the organism is rapidly destroyed by the phagocytes According to this theory *immunisation would consist in rendering* the 'receptive' cells resistant by desensitizing them with products derived from the particular bacteria The experimental evidence on which Besredka based his theory has been challenged His statement that after oral administration of dysentery or typhoid bacilli the agglutinins may appear in the blood of rabbits after the first administration but

a culture of anthrax bacillus ...
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... of ... rabbits produ...

injection

... applied his theory to ... vaccine ... by local

and to treat ...

applicat on of dressings saturated with filtrates of cultures of these organisms There is evi lence that the oral administration of typhoid vaccines does have some immunising value and we know that oral administration of living or dead bacteria is often followed by passage of antigen of the bacteria through the intestines and by the consequent production of antibodies The oral administration of vaccines is a less reliable and quantitatively very uncontrollable substitute for subcutaneous injection Regarding the local application of the so called anti virus preparations in the treatment of staphylococcal and streptococcal skin condition it would appear that the result is entirely non specific since infiltraton of the skin even with sterile broth raises the local resistance

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is to be lo
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30 hours the
but were recovered from the towel that had been allowed to dry Khines showed that *Myco tuberculosis* multiplied in sterile soil but in non sterile soil it was destroyed Frost proved that saprophytes in the soil produce substances that not only inhibit the growth of pathogens but bring about their destruction

The antagonist organisms described so far can be divided into four groups Th...

The ... *oides*
and *B* ... d and
cholera ... olated
Gramic ... with
large m... when
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neutralize the toxins Vaccines have a limited application in the *treatment of* disease but their prophylactic value in a number of infectious diseases is a great asset The specific immune therapy may either be active or passive The object of the active immunisation is the specific stimulation of the natural immunity *mechanism of the body through the* inoculation of a suitable suspension of the causative agent of the disease *vaccine therapy* Passive immunity aims at the destruction of the infecting organism or the neutralisation of its toxins through the inoculation of ready made specific substances or antibodies which are present in the sera of immunised animals *serum therapy* These two measures are suited for different types of diseases and when appropriately used they produce favourable therapeutic results Serum therapy has been found invaluable *in certain acute infections where a rapid neutralisation of the poison* is indicated and where it is desired to aid the overtaxed immunity mechanism of the patient Vaccine therapy on the other hand has been of benefit in prophylaxis and in treatment of a number of chronic localised infections where the patient is not too ill and his immunity mechanism is not exhausted But unfortunately at the present time, because of the growing tendency to apply these remedies in all sorts of unsuitable conditions both forms of specific immune therapy in general and vaccine therapy in particular have fallen into disrepute. In many instances the practitioner employs vaccine therapy not because he considers it suitable but because other remedies have failed and he cannot think of anything better The common excuse is that if vaccines do no good at least they do no harm This appears illogical as we believe that any remedy that has potentialities for doing good also possesses the power to do harm if improperly used The unscientific attitude the commercial exploitation of vaccine therapy and the utter disregard of the results which observation and experiment have made available are to be greatly deprecated The improper application of the therapy will only retard the progress of science and will help neither patient nor practitioner It is the clear duty of the medical practitioner by study and knowledge *of the latest advances in immunology* and bacteriology and through the proper and scientific application of these valuable therapeutic agents to contribute towards the progress of science and thus to the ultimate well being of the community The best thing for the practitioner to do is to use only those immunising reagents which have been shown *to possess definite protective value* under adequately controlled and extensive trials

3 Vaccine Therapy

[illegible] Cow pox was called *vaccinia* [illegible] inoculation against small pox [illegible] d to Jenner s nomenclature and applied the term *vaccine* to the suspensions of attenuated and killed bacteria that he used for immunisation At present the term *vaccine* may be defined as a suspension of killed or attenuated organisms or their products which when *inoculated into the body* stimulates the tissues to produce anti bodies which directly or indirectly bring about the destruction of the invading organisms and the neutralisation of the poison that the organisms may have produced

Va[illegible] [illegible]herapy has been in practice for a considerable length of time In ancient [illegible]

against small pox Although he could not explain the mechanism involved in the process

virulent organisms, and inoculating them into animals immunity might be produced He

Salmon and Smith (1884-86) were the first to show that injection of dead cultures of bacteria were capable of establishing immunity in animals But it was not till the work of Haffkine, Pfeiffer, Kolle and Wright, several years later that the modern method of prophylactic vaccination in man was well established Wright and his colleagues advocated its use for curative purposes, and according to them the justification for curative vaccination lay in the fact 'that in many instances infections are localised and that while the local capacities of resistance may have been lowered, the immunity mechanism in other parts of the body may not have been brought into play and that vaccines by stimulating these may flood the focus of infection with antibodies and phagocytes and overpower the causative agent' The experience gained during the past fifty years has vindicated in a convincing manner the value of vaccine therapy specially in the prophylaxis of the disease

A considerable amount of controversy has taken place as to the comparative value of living attenuated vaccine and vaccines prepared from killed cultures Considering that a certain amount of risk is attended with the use of living organisms for this purpose the general opinion is in favour of the use of vaccines prepared from killed cultures

(1) Preparation of vaccines

The selection of strains for the preparation of vaccines is of paramount importance in view of recent knowledge of bacterial variation and the associated changes in antigenic structure of the bacteria It is most essential to use a strain containing antigens which can be reasonably expected to confer active immunity against the particular infective disease From this point of view two types of variations are of great significance One is the 'S & R' variation and the other the 'H & 'O' variation

the production of protective vaccines is concerned In view of this it is essential that in the preparation of vaccines 'R' variants should be rigidly excluded

Smith and Reagh (1903) demonstrated the difference in the agglutination reactions

Medium Solid medium is better than liquid medium, it yields more growth and n constituents of the medium are included In liquid medium autolysates of the organism which are generally toxic and produce reaction are generally included Enrichment of th medium is permissible but no horse serum should be added to avoid serum sensitivity

In diseases like small pox and rabies the causative agent (filtrable virus) cannot be grown in culture media Therefore to prepare vaccines of these viruses they are cultivated in the tissues of animals (on the shaved skin of the abdomen of healthy calves in the cas of small pox virus and in the brain of sheep in the case of rabies virus) and an emulsio of the infected tissues made and tested for purity bacteriologically The preparation an standard sation of these vaccines require great care and technical skill and in some countrie a license has to be obtained for preparing these and only well equipped laboratories of first class nature are granted permission to manufacture them

Many of the viruses can be grown in chick's embryo and vaccines for prophylacti purposes have been prepared For the preparation of vaccines which consist of the exotoxi or endotoxin of organisms, as for example, Koch's tuberculin, diphtheria tetanus etc. th organisms are grown in special fluid media and when the maximum degree of toxicity i reached the medium is filtered, the bacterium free filtrate standardised and vaccine prepare from it

Time of growth before harvesting For economy try to get as much growth as possible but as a general rule incubation should be for 18 to 24 hours In prolonged incubatio autolysis comes in, which is not desired and in certain cases the organism changes *e g* in mucoid streptococci the capsule disappears after sometime

Maintenance of strain The strain properly
on a suitable medium The stock might also b
of the typhoid bacillus occasional mouse passag
preparation of a vaccine from a stock culture,
and purity tests should be repeated

Harvesting and *suspension* Add saline to each bottle, set for a while, then by rockin most of the growth will be washed off A stainless steel rod terminating in a triangula loop, or some other such gadget can be used for scraping Be careful to just scrape onl the growth and not to break the surface of the medium or get any particles of it in th suspension

be got rid of Autolysi
imes flagella and capsul
complaints of reactions

Enumeration In principle the methods used for enumeration may be classified a those of —

(1) Direct enumeration in a counting chamber
(2) Indirect enumeration
 (a) Wright's method
 (b) Colony count by making pour plates of differnt dilutions of the suspension
(3) Physical measurements
 (a) Weight of dried bacteria
 (b) Volume of bacteria
(4) Chemical measurement
 (a) Total nitrogen determination of the suspension micro Kjeldehal method recomended by Mueller is the best
(5) Turbidity measurements
 (a) Opacimetric
 (b) Nephelometric
 (c) Photometric
 (d) Photo electric

No matter what method is adopted for standardizing vaccine the result is expressed in millions of bacteria per ccm The counts of organisms fail to take into consideration the size of the organism therefore, the antigenic content will be better represented by ... of mg or the dried weight of bacteria As antigens are closely associated with proteins

easure of the amount
tter, for the sake of
popular methods at
Gates apparatus or
its modification are used in various places or comparisons are made with standard suspensions such as Brown's opacity tubes Bayliss has proposed a photometric method, and recently photoelectric cell has been utilized for determining turbidities of bacterial suspensions

Standardization. The antigenic value can be measured by protection test in mice or
imple for illustration 0 5 ccm
a mice against a lethal dose
B with mucin are lethal for
to be of much use

In rabbits living Vi bacilli produce Vi agglutinin titre that runs approximately parallel with the protective power against living virulent bacilli, and the O agglutinin titre runs parallel with the protective power against the toxic action of killed typhoid bacilli. The protective power of a vaccine can be judged by its capacity to induce the formation of Vi and O agglutinins in rabbits and finally in man This is simpler than protection experiment in mice The popular use of these methods is strongly suggested

Killing and preserving Heat is mostly used for killing and chemicals for preserving When heat is applied it should be the lowest temperature at which one is sure to kill the organism Generally 53°C for 70 minutes is quite enough Amongst the chemicals phenol formalin mercurials tricresol, and alcohol, etc, have been used Recently for typhoid vaccine Felix has recommended killing the bacteria with 75 per cent alcohol removing it and preserving it in 25 per cent alcohol in saline In his opinion alcohol is the best preservative for Vi antigen

The last step is to test for sterility before dispensing Most of the vaccines if kept under proper conditions are considered satisfactory for use for 9 months to a year from the date of preparation.

In 1908 Calmette isolated a strain ...
then on a medium
largely lost its capac
capable of producing
Calmette Guerin)
subcutaneously calv
kill normal animals within two months Innumerable trials have been made with B C G in animals and human beings Irvine had reviewed the literature up to 1934. He concluded that the virulence of B C G is not fixed although it had not been proved to have caused disease in man it might rarely produce progressive tuberculosis in animals As far as its value as an immunizing agent is concerned it produced in cattle a definite degree of immunity and in man it seemed to have increased the resistance but not so clearly Park and Kereszturi in America are of opinion that the virulence of B C G by residence in the human body is not increased and their opinion is shared by the majority Their data indicates that resistance to tuberculosis is considerably increased and they advocate its use in possible contacts who are not yet infected like new born children in a family with a tubercular member Others are against its use because of the troublesome small cold abscesses that may persist for months at the site of inoculation There is also chance however remote of its becoming more virulent Hahiff recently tried a heat killed vaccine in Jamaica The mortality in non vaccinated was 9 9 per cent and among the vaccinated 3 7 per cent In view of these results with killed vaccine we might conclude that B C G definitely increases the resistance to a moderate degree but is not decisively superior to killed vaccines The protective value of B C G in nontuberculin reactors has in recent years been established beyond all reasonable doubt as a result of millions of vaccinations all over Europe and America

(2) Varieties of vaccines

vaccine are alive and not dead
The
ie because there is experimental
proo
In the prevention of small pox
the
that the vaccine used is a 'live
vacc
vaccine in gonorrhoea, but his results are not encouraging While there are advantages in using a 'live' vaccine the procedure is attended with grave risks and, therefore, cannot be recommended as safe for employment in human

Sensitised vaccines These were originally introduced by Besredka, and are prep ly growing the organism ... priate imm ... entrifugal ... The vacc ... By sensiti ... is said to be enhanced because lar doses can be given and there is very little reaction after injection The preparation sensitised vaccine is not only difficult and expensive but it is also not possible for organisms It can be made only in those cases where a potent specific anti serum is availa It is commonly used in streptococcal infections and is well tolerated even by patients suffer from acute and generalised infections

Autogenous vaccines These are vaccines prepared from the organism causing infection in the patient Here one is certain that the vaccine prepared is antigenica specific and will give rise to antibodies that will produce maximum good to the patie Wherever possible autogenous vaccine made by a competent bacteriologist should be used

Formolized vaccines ha... a powerful toxin It has ... property but retain the antig ... Broth cultures or saline su... formalin which procedure kills the bacteria and where exotoxin exists converts it into nonpoisonous toxoid but still retaining its antigenic properties It has been used w success in the case of Shiga s dysentery bacillus The formol toxoid now so largely us for immunisation in diphtheria is produced by incubating a toxic filtrate with 0.4 per ce formalin for several weeks.

Defatted vaccines Douglas and Fleming (1921) claimed that a tryptic digest ... bercle vacci ... *He cla me* ... nical trial ... ot show ar advantage of this type of vaccine over the ordinary vaccines

Lipo vaccines In these the bacteria are suspended in an oily medium so that th vaccine substance would be slowly absorbed and the antibody producing stimulus would b prolonged thus approaching more nearly the condition in an actual infection The availabl evidence goes to show that these are less effective than the ordinary vaccine suspende in saline solution

Vaccines killed by chemical substances Vaccines killed with various chemicals sucl as ether iodine, and sodium fluoride have been extensively used in France with the ide that these not only kill the vegetative forms of bacteria but also detoxicate them bu they have not found favour anywhere else

Bacterial extracts filtrates and digests With the idea that antigen in solution can react immediately with the body cells thus enhancing the immunisation process such extracts have been used Although these are antigenic there is as yet no evidence to show that they are superior or even equal to the simple bacterial vaccine

Anti viruses These were introduced by Besredka (1919-24) with the idea that filtrates of cultures which have stopped growing contain inhibitory substances to which he gave the name 'antivirus' He claims that animals inoculated subcutaneously or intradermally or poulticed on their shaved skin with staphylococcal or streptococcal antiviruses are resistant to inoculation of virulent cultures introduced 24 to 48 hours later But this has not been substantiated by other workers

(3) Methods of administration

Vaccines are administered by the following routes —

Subcutaneous—This is the route commonly chosen Vaccines are best given at a point where the tissues are loose The popular site is the outer aspect of the arm about one-third of the distance down from the shoulder to the elbow

When large quantities have to be given as in antirabic treatment the sides of the abdomen may be preferable In the case of localised lesions some believe that injection of the vaccine near the lesion is more advantageous but there is no evidence in support of it

Intravenous Vaccines are sometimes given intravenously for the purpose of eliciting marked reactions In the treatment of arthritis typhoid coli and gonococcal infections vaccines have been given in this way The beneficial results noticed appear to be due to non specific protein reaction that follows This route is not however satisfactory for routine use due to presence of particulate matter in vaccines and due to the danger of producing protein shock.

Oral vaccines have been given by the oral route specially in little children and in patients who cannot overcome their antipathy to inoculations Besredka s bili vaccines are prepared specially for oral administration

When vaccines are given orally there may be certain amount of absorption of antigens through the intestinal mucosa with the consequent production of a certain amount of antibodies. But the immunity thus produced can never be expected to reach the level attained after say a subcutaneous injection and it is doubtful if it is efficacious at all

Intracutaneous Small pox vaccine is used in this way The cleaned skin is scratched gently by a needle or lancet care being taken not to draw blood and then vaccine lymph is applied to the scarified part and allowed to dry Some prefer to give bacterial vaccines also by this route but the advantages claimed are of doubtful value

Dosage Dosage varies not only with the nature of the vaccine used but also with factors such as age of the patient nature of the illness toxicity of the organisms sensitiveness of the tissue affected route of administration and the purpose of administration In young children in acute illness when sensitive tissues like the lungs or the brain are involved when the selected route of administration is intravenous or the purpose for which it is used is for cure of illness the dosage has necessarily to be small On the other hand in

interval between doses is given for chronic or subacute infections and 48 to 72 hours interval in acute cases but there is no hard and fast rule and the reaction of the patient is

Reaction following administration—Local focal and general reactions may be noticed after vaccine administration The first is characterised by pain, swelling redness and heat at the site of inoculation the second by exacerbation

constitutional disturbances because the local and general reaction play no part in the production of immunity The initial dose being a trial one, there may occur some slight focal reaction but this should not be allowed to recur Focal reaction is of a mild nature and disappears spontaneously

(4) Therapeutic uses

The most convincing results have been obtained by the use of vaccine for prophylactic purposes There is little doubt about the efficacy of preventive inoculation in small pox, rabies diphtheria scarlet fever cholera typhoid fever and plague As regards diseases such as influenza whooping cough and typhus,

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Formolized vaccines have been used in cases where the culture of the organism produces a powerful toxin It has been shown that toxins treated with formalin lose the toxic property but retain the antigenic property This principle has been applied to whole cultures Broth cultures or saline suspensions of organisms are incubated with 0.2 to 0.5 per cent formalin which procedure kills the bacteria and where exotoxin exists, converts it into a nonpoisonous toxoid but still retaining its antigenic properties It has been used with success in the case of Shiga's dysentery bacillus. The formol toxoid now so largely used for immunisation in diphtheria is produced by incubating a toxic filtrate with 0.4 per cent formalin for several weeks

Defatted vaccines Douglas and Fleming (1921) claimed that a tryptic digest of acetone extracted bacteria furnished a good antigen Dreyer (1924) prepared tubercle vaccine by first boiling the organisms in formalin and then extracting them with acetone He claimed to have cured tuberculosis in guinea pigs with the use of such a vaccine Clinical trial in man appeared to be favourable in the beginning but later observation did not show any advantage of this type of vaccine over the ordinary vaccines

Lipo vaccines In these the bacteria are suspended in an oily medium so that the vaccine substance would be slowly absorbed and the antibody producing stimulus would be prolonged thus approaching more nearly the condition in an actual infection The available evidence goes to show that these are less effective than the ordinary vaccine suspended in saline solution

Vaccines killed by chemical substances Vaccines killed with various chemicals such as ether, iodine, and sodium fluoride have been extensively used in France with the idea that these not only kill the vegetative forms of bacteria but also detoxicate them but they have not found favour anywhere else

n non react

Autolysates Sometimes the breaking down process proceeds too far and the immunising power of the vaccine is lost. More work is needed in this direction before this type of vaccine can be advocated for general use In this connection it may be stated that bacteriophage is really a combination of bacteriophage and vaccine

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Dosage Dosage varies not only with the nature of the vaccine used but also with

experimental dose and the subsequent doses must be controlled by the local focal and general symptoms The production of any marked reaction either local or constitutional after an injection may be considered a contraindication to any increase in dosage The time interval is another important factor to be considered As a rule 3 to 5 days or 7 days' interval between doses is given for chronic or subacute infections and 48 to 72 hours'

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(4) Therapeutic uses

The most convincing results have been obtained by the use of vaccine for prophylactic purposes There is little doubt about the efficacy of preventive inoculation in small pox, rabies, diphtheria, scarlet fever, cholera typhoid fever, and plague As regards diseases such as influenza, whooping cough and typhus,

the results are encouraging On the other hand the therapeutic use of vaccine has not been very successful so far, but lately they have been used more extensively with greater success on account of the better method of preparation. The success depends not only on the proper preparation of vaccines but also on the proper choice of cases When a course of an autogenous vaccine fails to produce

focus or those isolated are of no use as vaccines In these cases, the best results are obtained with stock vaccines The advantages of autogenous and stock vaccines have already been discussed

In some cases it is not enough to stimulate the defence mechanism of the body by vaccines alone but steps should be taken to ensure phagocytosis and the access of antibodies to the foci of infection For example in the case of chronic abscesses vaccines by themselves will do no good unless the abscess is opened and evacuated as well It cannot be overemphasized that a properly prepared vaccine should be considered as a potent substance capable of causing much harm to the patient when wrongly used Before the administration of a vaccine all these points should be carefully considered In competent hands results are very encouraging in cases of localised infections and evidence is gradually accumulating to show that vaccine may also do good in generalised infections as well

The following is a brief outline of the more important vaccines used either in prophylaxis or treatment of diseases

Typhoid Vaccine This is a mixed vaccine consisting of a carbolised saline

Vi antigen and produces better immunity

For prophylaxis it is given subcutaneously in two doses of 0 5 ccm and 1 ccm at an interval of 7 to 10 days Some prefer to give a third injection after 7 to 10 days For children the dose is proportionately reduced according to age

This vaccine has been used extensively in the British Army since 1909 with very good results The immunity lasts for about a year and revaccination with a single dose of 1 ccm should be done every year Intravenous inoculation of typhoid vaccine has been tried recently with very encouraging results The immunity is said to last longer in these cases but owing to the danger of protein shock this method is not recommended

Oral administration of vaccine has been extensively used in South Africa The vaccine is given as a suspension in teaspoonful doses or it can be made into a pill *Three doses* each of 45 000 million organisms combined with ox bile in keratine-coated pills can be given The results of oral administration however are inconclusive

In the treatment of typhoid fever vaccines have been used with some success An initial dose containing 100 millon organisms is given subcutaneously and subsequently three to four days apart the dose is increased gradually if sensitized vaccine is used this *should be given* daily for four days in doses of 500 to 1 000 million organisms subcutaneously or From the available evidence it appears that typhoid vacci of the disease but it has been argued that the s any other bacterial vaccine and that the action obt haracter

Bacillary dysentery Two types of organism are mainly concerned in this infection *Bact shigae* and *Bact flexneri* *Bact shigae* is a very toxic organism producing an exotoxin whereas *Bact flexneri* is relatively non toxic On account of the toxicity of the Shiga type various attempts have been made to reduce the toxicity of these strains for the preparation of vaccine

Recently formolised vaccine (anacultures) have been used with success but it has not as yet been tried extensively enough to enable one to assess its real value in prophylaxis Vaccination against dysentery with oral administration of Besredka s bilivaccine is recorded to have given good results but they are not so uniform as in the case of subcutaneous injection

In the case of *Bact flexneri* the preparation of a vaccine is much less difficult as it is nontoxic Except that the vaccine should contain all the representatives of various antigenic groups there is no other precaution necessary in the preparation of the vaccine The usual prophylactic dose is 250 500 and 500 millions at weekly intervals

Treatment of bacillary dysentery by means of vaccines is used especially in chronic cases Opinions as to the efficacy of vaccine in such condition are very divergent but Nolf (1919) and Acton and Knowles (1924) report favourable results with autogenous and stock vaccines

In the beginning vaccines may be given subcutaneously or intracutaneously starting with small doses such as 10 000 to 1 000 000 organisms and increasing to as high as 5 to 10 million organisms Some clinicians have reported striking results in chronic cases with intravenous doses every fourth or fifth day and gradually increased from 5 to 60 million organisms It has also been tried in combination with 150 to 200 ccm of water per rectum by the drop method Polyvalent vaccines have also been tried by the mouth Doses recommended are 20 to 30 drops on the first day 50 drops on the second day and 60 to 70 drops on the third day Vaccines in the form of tablets have been prepared for use during epidemics Each tablet contains 100,000 organisms and 5 or 6 tablets may be given daily dissolved in water or sodium chloride solution The results of vaccine treatment have varied greatly in the hands of different observers

Cholera vaccine It is only used for prophylactic purposes The vaccine consists of 24 hours culture of the cholera vibrio suspended in normal saline killed by heat at 56°C for half an hour and 0 5 per cent phenol added as a preservative Vaccines prepared in India contain 8,000 million organisms per ccm and the usual prophylactic doses are 0 5 ccm and 1 ccm at an interval of a week A third dose of 1 ccm may be given but is thought to be unnecessary Sometimes cholera vaccine is mixed with T A B vaccine to produce immunity against all simultaneously In emergency when two doses cannot be given a single dose of 8 000 millions will give rise to sufficient protection

In the prophylaxis of cholera extensive observations were made in India by Russell He found that in the comparative trial of cholera bilivaccine (oral) and the ordinary cholera vaccine (subcutaneous) both conferred a high degree of immunity Russell expressed the opinion that the subcutaneous method was superior and was able to show that five days after a single subcutaneous dose of cholera vaccine the immunity was about as high as that present three days after a full course of the oral vaccine

Plague vaccine Statistical evidence from different countries shows that vaccination against plague reduces the incidence and case mortality markedly

"*Formolised anti Plague Vaccine* (Plague Vaccine Haffkine s Plague Vaccine) — Formolised Anti plague vaccine is an uncontaminated culture of micro organisms *Pasteurella pestis* grown in liquid media *e g* acid hydrolysate of casein and killed by the addition of *formaldehyde* *It should have a minimum mouse protection dose of 0·004 mils or less*

It may be prepared in the following way A fresh sub-culture of *Pasteurella pestis* is selected which has been examined to ensure its identity and purity and which has been tested for virulence and antigenic efficiency by animal experiments The culture medium used is an acid hydrolysate of casein having a pH of 7 2 and a nitrogen content of 250 to 2 0 milligrammes per 100 millilitres A forty eight hour culture of the selected strain of *P pestis* is prepared in this medium in a Pasteur balloon flask and this is used to inoculate three litre Haffkine flasks each of which contains one litre of the acid hydrolysate medium The Haffkines flasks are inoculated at 28° for 15 days The cultures are then killed by the addition of solution of Formaldehyde in a concentration of 0 1 per cent which is allowed to remain for 7 days at 37° Tests for purity and sterility are carried out at appropriate stages du
preserved by the addition of
per 100 millilitres of the va
vaccine is distributed, under
are sealed so as to exclude bacteria "

The vaccine is a brownish turbid liquid with or without flakes or clumps It complies with the tests for sterility, and tests for freedom from abnormal toxicity Its potency is determined by the biological assay of plague vaccine Anti plague Vaccine should be stored at a temperature of 00° to 40° and should not be used later than three years after preparation

Lobar pneumonia—A considerable amount of work has been done in recent years on the value of vaccines in the prophylaxis and treatment of lobar pneumonia and workers are unanimous that administration of pneumococcal vaccine confers a high degree of immunity in susceptible animals The immunity is type specific so that in the preparation of a prophylactic vaccine all the common types have to be included According to the recent work of Griffith on the variability of the types of pneumococcus there is a possibility of change in types after repeated mass inoculation so that the vaccine has to be changed accordingly

Prophylactic vaccination for pneumonia has been extensively tried on the Rand mines in Africa with inconclusive results The trials in the army have also not produced convincing evidence in favour of prophylactic vaccination

As regards the treatment of lobar pneumonia with vaccine it has been seen that if administered early it influences the course of the disease so that combined with serum treatment it may be of great help Minor pneumococcal infections such as the common cold with bronchitis, chronic sinusitis and other nasal inflammations if unattended with any other pathological condition *e g* deviated nasal septum polypus etc are benefited by the administration of a pneumococcal vaccine Where possible autogenous vaccine should be employed but stock vaccine is also of benefit In the conditions the initial dose is 10 million organisms increased every 3 or 4 days, up to 100 millions after this it is increased by 100 millions at weekly intervals For prevention of exacerbations monthly injections of 100 millions should be continued during the winter

Whooping cough Results had been very variable with the use of this vaccine in the past when the importance of freshly isolated cultures was not recognised but with the use of fresh cultures the results have been very encouraging The vaccine must be prepared from an absolutely smooth virulent strain preferably a freshly isolated one The vaccine is usually prepared to contain 10000 million bacilli per ccm Four injections are given at an interval of 7 to 10 days The initial dose is 1 ccm the second and the third doses are 1 5 ccm each and the fourth dose is 3 ccm

For treatment mixed vaccines are better than vaccines consisting of only *H pertussis* A combination of 500 millions of *H pertussis* with 250 millions of *H influenzae* and 20-100 millions of pneumococci per ccm is very suitable. This is given every day or every 2 days to a child of five or six years in doses of from 0 2 ccm to 1 ccm Cockshut claims to have got extremely good results by the use of doses 4 to 10 times of those recommended

Infl ... is used formolised mouse adapted ... culture virus in America Human ... rations show a marked rise in a ... the field but the results in America appear to be hopeful

Acute rheumatic fever ... h hæmolytic streptococci has given favourable result ... which are so common in this condition Weekly ... ,000 cocci followed by 500 000 and then continued ... followed by a gradual increase by 10 millions till ... ccine was administered intravenously with safety

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The Arthritis Committee of the British Medical Association (1933) recommends an initial dose of 20 000 to 50 000 organisms when a septic focus is suspected or half a million when no septic focus exists The doses are gradually increased every five or six days and it is rarely that a case will require a dose of more than 10 millions

Acne vulgaris This condition is due to a mixed infection with the acne bacillus and the staphylococcus Vaccines prepared from both these organisms have been found to be of benefit in such conditions The treatment should be continued for a long time to get any good result Autogenous or stock vaccines may be used The stock vaccine should contain both types of organism

For therapeutic purposes mixed staphylococcus and acne vaccines are used The dose of staphylococci is from 200 millions gradually worked up to 2 000 millions Acne bacillus is best given in an initial dose of 5 millions followed at weekly intervals by doses of 7½ and 10 millions If there is no improvement with these the dose should be increased to 100 millions and should be followed by increases of 100 or 200 millions up to 2 000 millions As the acne bacillus is but slightly toxic and very seldom gives rise to general reactions these large doses can be given with safety Sometimes it is mixed with intestinal streptococci especially in cases where there is a preponderance of streptococci in the intestine The dose used is similar to that of the acne bacillus This treatment should of course be combined with suitable medicinal dietetic or physical treatment and regular evacuation of the contents of acne pustules and removal of comedones

Furunculosis [illegible]
by Wright Usuall [illegible]
is very little differe [illegible]
in the treatment of [illegible]
but it prevents the recurrence of this condition anywhere else in the body

Large doses are recommended for indolent boils to produce a focal reaction which is beneficial in such cases The usual dose in a severe case is 100 to 2 000 millions of staphylococcus In less severe cases 200 or 300 millions may be the initial dose increased at intervals of 5 to 7 days up to 1 000 or 2 000 millions Usually six to eight doses are sufficient to cure even very chronic cases But failing with this vaccine streptococci isolated from fæces or boils may be combined with this vaccine

Gratia (1930) has used a vaccine in which staphylococci were dissolved by certain streptothrices and moulds This he calls *mycolysates* which are very beneficial in chronic cases Bacteriophage lysed vaccines are also in use but the results so far are indifferent As a result of the recent isolation of a powerful exotoxin from staphylococci it is being used in modified form (toxoid) for the treatment of boils This toxoid is prepared by incubating the toxin with 0 3 per cent formalin for 2 days and injecting subcutaneously commencing with a do e of 0 05 ccm and increasing the dose every five to seven days by 0 05 ccm Although still in the experimental stage the results so far obtained are very encouraging

Coliform infections Bact coli vaccines are used both for prophylactic and curative purposes For prophylaxis they are used in patients suffering from coliform infections of the urinary tract preparatory to a major operation of the genito urinary tract Cases for such treatment should be carefully chosen as there may be acute symptoms of coli fever following an initial dose in cases where there is an obstruction to the outflow of urine The doses recommended are 100, 500 and 1 000 millions at weekly intervals

For therapeutic purposes these vaccines are used for cases of bacilluria and pyuria which are resistant to ordinary treatment and in which no exciting cause can be found

The initial dose in children over 5 years should be 20 millions increased at weekly intervals to 500 million organisms In adults the initial dose is 25 millions increased gradually at weekly intervals to 2 000 millions if there is no focal or general reaction Acute infections due to late fermenting coliform bacilli are also treated with such vaccines The initial dose of 25 millions should be given about 8 days after the temperature has returned to normal the dose being increased gradually to 500 or 600 millions at weekly intervals

Ulcerative colitis Recently a special type of diplococcus has been isolated from ulcers in cases of ulcerative colitis and vaccines prepared from such organisms either alone or combined with an antibacterial serum have been found to be of great benefit (Bargen 1924) The treatment however should be combined with strict attention to diet and removal of septic foci The vaccine is prepared by culturing the cocci in broth for 48 hours adding 0.4 per cent tricresol to the culture to sterilise it and the concentration adjusted to 2 000 millions per ccm

The vaccine is a brownish turbid liquid, with or without flakes or clumps It complies with the tests for sterility, and tests for freedom from abnormal toxicity Its potency is determined by the biological assay of plague vaccine. *Anti plague Vaccine should be* stored at a temperature of 00° to 40°, and should not be used later than three years after preparation '

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Acute rheumatic fever Vaccine treatment of this condition with hæmolytic streptococci *has given favourable results especially in checking the recurrences which are so common* in this condition Weekly doses are given commencing with 200,000 cocci followed by 500,000 and then continued as follows —1 2½ 5, 10 15 20 millions followed by a gradual increase by 10 millions till *100 millions have been given The vaccine was administered* intravenously with safety

Chronic rheumatic conditions These include various forms of non specific arthritis fibrositis perineuritis, etc Various attempts have been made to treat these cases with vaccines prepared from organisms isolated either from the site of the lesion or from a septic focus in the teeth, *tonsils nasal sinuses gen to urinary or intestinal tracts* Although it is very difficult to correlate the finding of organisms from such septic foci and the occurrence of rheumatic conditions yet it has been seen that vaccines prepared from them are able to alleviate or cure the condition in a large number of cases Vaccine treatment should be auxiliary to any radical measures necessary for the removal of an infected focus Autogenous vaccines are better than stock vaccines in these cases but the vaccine should be prepared by an expert A stock vaccine *for such conditions should* contain a large number of strains from the mouth, tonsils intestine and genito urinary tract isolated from rheumatic cases

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An initial dose of 200 millions is given and if it is not followed by any reaction the dose is increased every third day up to the maximum dose of *2,000 millions per ccm* Sterile filtrates of cultures of the organism have also been used the maximum dose being 1½ ccm of such filtrate

Gonococcal infections The use of such a vaccine has been of great value in cases of complications resulting from an infection with gonococci but used with caution *it can be helpful in all stages of gonorrhœa* In the early stages it reduces the duration of primary infection and diminishes the number and severity of the complications It is used in complications such as arthritis *epididymitis orchitis etc* Gonococci are composed of many antigenically varying members so that any vaccine to be of use should either be autogenous or should contain a large number of these strains

Various different vaccines have been used for the treatment of such conditions but most commonly used is the simple vaccine prepared *from freshly isolated cultures grown on* serum agar Mixed vaccines have been used in some cases consisting of staphylococcus streptococcus or diphtheroid bacillus along with polyvalent gonococcal vaccine

Only small doses are tolerated and it is best to avoid any reaction The dose also depends on the severity of the illness In acute complicated cases it is advisable to begin with 500 000 organisms and gradually work up to 10 millions In chronic cases the initial dose should be small but amount administered may rapidly be increased up to 500 millions or more so long as *there is no reaction*

Asthma True asthma is generally a [illegible] foreign protein *There are however, many cases in* [illegible] and it is in these cases that vaccine therapy [illegible] many workers Either autogenous or stock [illegible] organisms such as *H influenzae* pneumoco[illegible] obtained from sputum culture In a certain percentage of cases refractory to such vaccines *organisms isolated from the intestine particularly enterococci* are incorporated in the vaccines with great benefit In determining the sensitiveness to the various organisms isolated either from the sputum or intestine dermal reactions are of great help

The initial dose should always be small in order to prevent the precipitation of attack The initial dose of streptococci 0 1 to 0.5 million are used increased by 0 1 million up to 1 million and further continued where necessary to as large a dose as can be tolerated by the patient

If there is reaction with any dose the next one is reduced and further increase in dosage should be made with great caution Freeman advocates 0 5 ccm of adrenalin mixed *with the vaccine to avoid reactions*

Smallpox The vaccine used for prophylaxis is a living attenuated virus and of all *prophylactic vaccinations this* is perhaps the most useful Vaccination has very appreciably reduced the incidence and the mortality rate of smallpox

The vaccine is available *in this country only in government* laboratories and municipal vaccine depots It consists of a glycerine emulsion of scrapings of pustules from calves inoculated with the smallpox virus

The technique of vaccination The skin of the forearm or upper arm is cleaned with soap and hot water and dried with a clean towel (no antiseptic is used) Two drops of the vaccine lymph are placed on the site of inoculation and the part is gently scratched with a lancet over an area of half an inch by one third of an inch care being taken not to draw any blood A blunt body like a small saw has lately replaced the lancet in many places The excess of the lymph is allowed to dry on the skin

Rabies This vaccine has been found to be *very successful for prophylaxis* The principle of vaccination in this case is the immunization of the affected person during the *period of incubation* which is fairly long

[illegible]ies Vaccine Pasteur Treatment Semples [illegible]ontaminated suspension of brain substance [illegible]he addition of phenol

It may be prepared in the following way A suitable strain of rabies fixed virus is maintained by passage in rabbits Healthy animals (preferably, sheep) are inoculated sub durally with a suspension of the brain substance of a rabbit in which the fixed virus has been passaged When *the animal has died or has been killed* when moribund after showing characteristic symptoms of infection with rabies fixed virus the brain is removed *under asept c* conditions, is tested for absence of bacteria and is emulsified in physiological

solution of sodium chloride so as to form an 8 per cent suspension of brain substance. Phenol to make a concentration of 1 per cent is added and the concentrated suspension is incubated at 37° for 24 hours to kill the virus. The concentrated suspension is then diluted with physiological solution of sodium chloride to make a final concentration of 5 per cent brain substance and the phenol content is adjusted to 0.5 per cent. The finished vaccine is distributed under aseptic conditions into previously sterilised containers which are sealed so as to exclude bacteria.

It is a white or whitish more or less turbid liquid having a slight odour of phenol. It complies with the tests for sterility and tests for freedom from abnormal toxicity. Carbolised Anti Rabic Vaccine should be stored at a temperature between 2° to 10° preferably at the lower limit. It should not be issued for use until after the lapse of at least 10 days from the date of addition of phenol. A test for presence of phenol must be made before issue. (Indian Pharmacopoea List 1947)

Diphtheria.—In the past no method was known of immunizing children against diphtheria but with the increase in our knowledge on immunity various methods have been adopted for immunizing children against this disease. The formol toxoid and the alum precipitated toxoid are now used.

The recommendations of the Ministry of Health for immunization should be followed. They recommend that immunization should be preceded by a Schick test to exclude children who are already immune. Positive Schick reactors who have simultaneously been tested for hypersensitiveness to toxoid and found to be negative should be immunized by subcutaneous injection of formol toxoid in doses of 1 ccm on three occasions with fortnightly intervals. Another Schick test should be done some months after immunization to ascertain the development of immunity. The most suitable age for such immunization is between one and three years as very few children are hypersensitive to toxoid at this age and it is given at a period when they are most liable to infection. Children below one year need not be immunized.

Recently one shot method of immunisation and immunisation through instillation of the toxoid through the nose have been tried.

4. Serum Therapy

The practice of serum therapy began with the remarkable discovery of von Behring and Kitasato (1890) who showed that the sera of animals that had received injections of tetanus and diphtheria toxins had the property of neutralising these toxins and could prevent their poisonous effects. Following upon their discovery, Pfeiffer (1894) demonstrated that cholera vibrios when introduced into the peritoneal cavity of immunized guinea pigs, were killed and lysed. These observations lent support to the view that the blood sera of immunized animals contained protective substances which on being transferred to infected animals would help the latter to overcome the infection. Later on attempts were made to prepare antisera against various bacterial infections and they were tried in the cure and prophylaxis of the corresponding bacterial diseases.

Although it was hoped in the begining that antisera of high therapeutic value could be prepared against various bacterial infections by immunizing animals the experience of the past four decades has proved to the contrary. The reasons are not far to seek. There are various virus diseases *viz*, chicken pox, measles etc. where the pathogenic organisms have not been culturally isolated *in suitable antigenic forms* while there are others, *viz*, typhoid, cholera etc, in which though pathogenic organisms can be isolated they fail to produce antisera of any therapeutic value.

A careful study of the available data reveals that the value of antisera varies with the type of the serum (whether antitoxic or antibacterial) and the time of administration in the course of the disease. For prophylaxis the usefulness of antisera seems to be limited. The protection they afford is only for a short period (4 to 6 weeks) owing to the rapid elimination and disappearance

of antibodies from the blood As a therapeutic agent the use of antitoxins is extremely helpful especially in diseases like diphtheria where the toxin circulating in the blood is directly neutralised by the antitoxin provided it is given early and in adequate dosage

On the other hand antibacterial sera are not of as much prophylactic or therapeutic value as the antitoxic This is because such sera act partly by the presence of specific bacteriolysins opsonins etc and partly by the mobilisation of the nonspecific immunity mechanism Hence a higher concentration of antibodies in the serum does not necessarily mean greater efficiency Still the administration of potent antibacterial sera in the early stages of severe bacterial infections such as Felton's antipneumococcus *serum in type I pneumonia* polyvalent antimeningococcus serum in cerebro spinal meningitis in most cases cuts short the course of the disease and prevents unfavourable complications It may hence be concluded that although the sphere of usefulness of antibacterial sera is limited they are of considerable therapeutic value in certain selected cases

Types and preparation of antisera The antisera in common use may be divided into three types

(1) Antitoxic sera (2) antibacterial sera (3) antiviral sera

The methods of preparation of these are different and may be described briefly as follows —

Antitoxic sera. These are prepared by immunizing horses by repeated inoculations of formolised toxins (0 2 to 0 4 per cent of formalin added to the *crude toxic filtrate and incubated at 37°C for from 4 to 6 weeks)* The serum is obtained from such animals and standardised in terms of antitoxic units as prescribed by the official control authorities such as the Permanent Commission of the Health Organisation of the League of Nations Official control also exists in most of the countries to regulate the standard of purity and potency *of therapeutic sera The important and frequently used antitoxic sera are* etanus diphtheria gas gangrene antivenin etc

Antibacterial sera These are prepared by immunizing horses or other suitable animals by repeated inoculations of organisms The antigen in this case *consists of a suspension in* physiological saline of the bacterium either living or killed which contains both bacterial protein and endotoxin The serum of [illegible] animals contains antibodies against both According to our recent [illegible] in certain types of organism and the extreme [illegible] isera prepared from such antigen great care [illegible] *t antigen in the preparation of these antisera* In the preparation of a polyvalent antiserum the different type specific sera are prepared separately and then are mixed together The titration of such sera is done by estimating the different antibodies *e g* agglutinins complement fixing antibodies etc or by animal experiments Examples of sera mainly antibacterial are the *antistreptococcal anti dysenteric anti pneumococcal* anti meningococcal anti plague, etc

Antiviral Sera There is ample evidence to show that immune bodies capable of neutralising the virus appear in the blood during the course of virus infections such as measles *poliomyelitis* etc These immune bodies can exert a prophylactic and some curative action Convalescent sera have therefore been used in the prophylaxis and treatment of such diseases with favourable results specially in prophylaxis

Patients free from tuberculosis syphilis or other infectious diseases are selected for this purpose and 500 ccm of blood from an adult or 100 ccm of blood from a child are obtained under sterile conditions the serum separated filtered and preserved by addition of 0 5 per cent carbolic acid or 0 39 per cent of tricresol If kept in an ice chest these sera retain potency for months In measles in addition to serum from convalescent patients serum from normal adults who have previously suffered from the disease has been used with considerable success In view of the difficulty of getting large amounts of convalescent measles serum the observation is of great value Normal adult serum has been tried for prophylaxis of measles but it is too early to evaluate the results For prophylaxis purposes the convalescent or the normal adult serum is given intramuscularly within 5 days of exposure to infection and it is practically of no value if not given till 9 days after exposure The dose of the convalescent serum in ccm is calculated by multiplying the age with 2 of the normal adult serum by multiplying the age with 4 For treatment the serum is administered by intravenous route and must be given within 6 days of onset For prophylaxis of poliomyelitis 10 ccm of convalescent serum is injected subcutaneously or intramuscularly into young children who have been exposed to infection The injection should be repeated after a month if the epidemic persists

Convalescent smallpox serum has been used with promising results in cases of encephalitis following vaccination It has also proved to be possible to immunize animals against virus infections and thereby to obtain a serum capable of influencing the course of the disease against which the animal has been immunized

The concentration of sera It has been found that the bulk of the antitoxin is associated with the pseudoglobulin fraction of the protein whereas protective substances in antibacterial and antiviral sera are mainly associated with the euglobulin fraction The different proteins of the serum the euglobulin the pseudoglobulin and the albumin have different degrees of solubility in neutral salts By adding appropriate concentrations of ammonium or sodium sulphate to the serum or plasma different serum protein fractions can be separated for the purpose of concentration and purification of the sera The advantage of such concentration and purification is that considerably larger quantities can be administered without the risk of foreign protein shock

Storage and deterioration of sera Sera must be kept in the dark and in the cold The potency of most sera is maintained for a period varying from a year to two years after which there is a decline in the number of units of antitoxin in it and if due allowance is made for this deterioration sera may be used which have kept for periods longer than the time limit on the labels

(1) Modes of administration

The choice of the route by which an antiserum should be administered is a very important consideration because upon it depends the rapidity of absorption of antitoxin or other antibodies For prophylaxis where rapid absorption is not a necessity antisera are usually administered subcutaneously But the proper choice of route in the therapeutic use of an antiserum is of the greatest importance The various routes most commonly chosen are subcutaneous intramuscular intravenous intrathecal and other less commonly used routes are intraperitoneal intracisternal intraventricular oral and rectal The best route to

be adopted in a particular case depends on the nature of the illness and the type of the antiserum, the severity of the illness the stage of the disease at which antiserum is being administered, the age of the patient, etc

Subcutaneous This is the route commonly used although it is neither the best nor the most effective for prophylaxis it is used very commonly For therapeutic purposes particularly in severe *toxæmic cases where rapid neutralisation* of toxins is desirable it is useless because the antibodies inoculated are absorbed too slowly to attain quickly the necessary concentration in the blood The belief that this route is safer than the intravenous route has not also been substantiated by experimental evidence

Intramuscular This route is preferable to the subcutaneous and should be more widely practised When sera are given by this route antibodies are rapidly absorbed and reach a high concentration in the blood in a comparatively short time

Intravenous This is the best route for administration of antitoxin where the aim is to get a direct neutralisation of the toxins circulating in the blood In acute and severe cases where toxæmia is great and delay dangerous the initial doses of serum should be given intravenously as a routine procedure followed by intramuscular or subcutaneous injections for the subsequent doses Experience has shown that this route is not generally more risky than others if the serum is given diluted with normal saline and at body temperature

Intrathecal This route is preferable in diseases such as cerebrospinal fever tetanus and poliomyelitis *where it is desired to obtain the highest concentration of antibodies in* the focus of infection A lumbar puncture *is performed under local anæsthesia and an* amount of cerebrospinal fluid equal to or slightly more than the amount of serum to be injected removed and the serum allowed to run into the theca by gravity or by injection with a syringe The quantity of serum given at a time is generally 20 to 30 ccm for an adult

Intraperitoneal Plateau (1923) used this route in severe cases of diphtheria in infants where it was difficult to obtain suitable veins for intravenous injection It has also been recommended by other workers and is said to be safe and well tolerated by the patients but it has not been used much on account of the apparent risk of trauma or sepsis

Intracisternal [illegible]
extent especially [illegible]
1931) It appear [illegible]
practice on the c[illegible]
block.

Intraventricular This method has not been much used and it is *doubtful* whether the results are encouraging Neal prefers th[illegible]
block In young infants ventricular p[illegible]
fontanelle and the method is particularly [illegible]
[illegible] t has been shown [illegible] the least effective
spe[illegible]
If [illegible] n should be diluted
and [illegible]

Rectal This route although equally ineffective is sometimes chosen to avoid serum reactions and discomfort following repeated inoculations The rectum is cleared by an enema the serum *diluted with normal* saline made up to about 4 to 5 oz warmed to body temperature and given high up with the help of a catheter

(2) Reactions following administration of serum

Parenteral administration of a foreign protein is sometimes followed by certain reactions These are usually of moderate severity and do not constitute any danger to life The factors that bring about such unpleasant reactions are bound up in part with the serum irrespective of the specific antibody it may contain and in part with the degree of sensitiveness to the foreign protein of the person *receiving it* The following are the common reactions met with

In most cases the injection of antiserum is followed by only slight reactions such as local pain and tenderness accompanied by mild fever which passes off in 24 to 48 hours In a small *percentage of cases* however more severe reactions may follow

Protein shock This is generally observed after intravenous injections of large quantities of serum and is ascribed to the effect of foreign protein introduced
by chill dysp
temperature t
symptoms generally pass off without any treatment, but when they persist an injection of adrenalin 0 5 ccm or atropine 1/120 gr subcutaneously is all that is needed to restore the patient to normal

Serum sickness This complication is seen in some persons about 8 to 10 days and sometimes even earlier after the injection of serum It is characterised by urticarial rash pruritus pyrexia swellings of joints and lymphatic glands malaise œdema and albuminuria The incidence and severity of serum sickness increase with the age of the patient The frequency of reaction is said to be less after intravenous than after intramuscular injections and serum of some horses is particularly liable to produce these reactions The reason for this is unknown The reaction is rarely severe and needs only symptomatic treatment Calcium lactate in 10 gr doses 3 or 4 times a day is beneficial antipruritic lotions such as calamine lotion with 1 0 per cent carbolic acid relieve itching aspirin 5 to 10 gr by the mouth reduces pain and pyrexia When it is intended to give large doses it is advisable in order to avoid these unpleasant complications to use concentrated sera in preference to ordinary sera The incidence of this condition has been considerably reduced since the introduction of concentrated sera

Anaphylaxis This is one of the dreaded dangers that often dissuades the practitioner from using serum or giving it by the intravenous route Anaphylaxis has undoubtedly been the cause of some fatalities but it should be realised that the likelihood of its occurrence is remote its incidence according to Park (1928) being only 1 in 20 000 and fatality 1 in 50 000 It can be avoided if a little care is taken and the case is studied before injection

Some persons are extremely sensitive to the administration of a serum These may be divided into two groups

(a) Carriers of an hereditary allergic factor *e g* horse asthmatics who react almost immediately following the administration of a dose of serum

(b) Persons sensitized b[illegible]

[illegible] Although there is no risk of death the symptoms are sometimes alarming characterised by a sudden onset about a quarter of an hour after the introduction of the serum with restlessness anxious expression pallor perspiration rapid feeble pulse deep and laboured respiration followed by cyanosis unconsciousness muscular twitchings rigors convulsions and involuntary micturition and defæcation For this reason it is necessary to test the sensitiveness of a patient by intracutaneous injections of 0 05 ccm of 1 in 10 diluted serum If after 10 to 20 minutes the resulting wheal increases in size and shows a zone of erythema the reaction should be considered positive The degree of sensitivity depends on the extent of the wheal and reactions with pseudopodial projections are indicative of an extreme degree of sensitiveness In America the conjunctival test is preferred to the intracutaneous test It is said to be a more sensitive test but unfortunately is associated with the risk of damaging the cornea in hypersensitive subjects

In the therapeutic treatment of tetanus therefore large repeated doses of the serum are required The serum should be given by intramuscular, intravenous and intrathecal routes There is evidence to show that the injection into the cisterna magna gives better results than the lumbar puncture route

Antistreptococcus Serum There are two different types of sera antitoxic and antibacterial to be considered under this heading The antitoxic serum is produced by immunising horses with erythrogenic toxin of *Str pyogenes and is known as the anti scarlatinal serum* The ordinary antistreptococcal sera are prepared by immunising horses against killed cultures of streptococci

Antiscarlatinal Serum It is used in the treatment of scarlet fever It is a specific antitoxic serum and on a priori ground one would expect that its administration will have an effect only on those manifestations of the disease *which are toxic in origin and* will have no effect in those complications such as otitis and adenitis which are caused by the massive spread of hæmolytic streptococci There is evidence to show that the serum actually has *a significant therapeutic effect on toxic manifestation* of the disease as it decreases the death rate in severe cases and diminishes the toxaemic symptoms in milder cases As regards its effect in reducing the frequency of complications most of the *observers did not notice any such effect But* others found that the frequency of these complications was considerably reduced

The antiscarlatinal *serum the chief effect of which is to neutralise the erythrogenic* toxin can not be expected to do any good in diseases such as puerperal fever cellulitis etc *Which are caused by the invasive spread of hæmolytic streptococcus*

Antistreptococcal serum This serum is used in the treatment of puerperal fever cellulitis erysipelas endocarditis etc The existence of a large number of antigenic types of the hæmolytic streptococcus makes it essential that to be of any use the serum should be type specific *i e,* it should contain antibodies corresponding to the surface antigen of the infecting type just as we use type specific sera in the treatment of *pneumococcal pneumonia Since such type-specific antistreptococcal* sera are not available there is no scientific basis for using the available antibacterial sera in the treatment of diseases caused by invasive spread of hæmolytic streptococci The results of clinical *trials have on the whole been rather disappointing*

Antidysentery serum The chief bacterial species calling for serum treatment in the order of their *importance are the following —Bact shigae,* and *Bact flexner* Although there is some divergence of opinion on the efficacy of antidysentery serum there is considerable e [illegible] support to se The best results are obtained *with the Shig* [illegible] *the use of Flexner* serum also In the [illegible] the types of antigens such as V W X ([illegible] rses The Flexner serum consists of a [illegible] *is antitoxic* Some people are of opinio [illegible] is a sufficient amount of antibacterial [illegible] gh Shiga serum can be standardised *there is no method available to sta*[illegible] *xner serum*

Serum for therapeutic purposes should be given early (12 to 24 hours after the onset of symptoms) and in adequate dosage to get the best results In cases where the nature of the dysentery has not been diagnosed it is best to use a polyvalent serum In cases of ordinary severity a single injection *may be* followed by remarkable improvement but in severer cases the dose has to be repeated in from 12 to 24 hours and again in 48 hours In Shiga infection 3 000 to 4 000 units should be given in mild cases and 5 000 to 10 000 in more severe cases Serum in strength of 1 000 units per ccm is generally *obtainable but the more* concentrated preparations contain about 5,000 units per ccm The early stages of the disease are undoubtedly benefited by large doses of the serum and the death rate is low, but after the first week of the disease it is less effective and of *no value in chronic cases In* patients suffering from severe toxaemia the best results were obtained by intravenous injection of 60 to 80 ccm of the Shiga serum followed by 150 to 200 ccm of normal saline administered twice daily for the first two days and once daily *for the next two days In very toxic* cases 5 per cent glucose in distilled water is substituted for the saline In less severe cases the intramuscular route is preferable to the subcutaneous route, which is painful and the dose should not be less than 40 ccm in an adult and *as much as 100 ccm may* be given

High rectal injections of 10 to 30 ccm of polyvalent serum after cleansing the bowels with 1 5 per cent sodium bicarbonate and followed by starch and tincture of opium have also been tried. Intramuscular injections should be given *at the same time The varying* results given by the serum are probably due to the difficulty in standardising and the varying qualities of sera on the market

Antipneumococcus serum This serum is prepared by immunising horses with whole cultures of pneumococci The therapeutic effect of the antipneumococcal sera are strictly type specific Extensive trials with antisera in the treatment of lobar pneumonia suggest that type I antiserum significantly reduces the mortality rate of type I pneumonia that the results with type II antiserum in the treatment of type II pneumonia are less efficacious and that the type III antisera are quite ineffective Antisera against a few of the newer types (VII VIII and XIV) have been prepared but they have so far been used on too small a scale to allow any conclusions to be drawn It is essential therefore that if an antiserum has to be used in a case of lobar pneumonia the type of the infecting pneumococcus should be determined as early as possible To start with a polyvalent type I and type II antiserum should be given when the type of the infecting pneumococcus is determined and if it happens to belong to type I or type II the polyvalent serum may be replaced by the monovalent serum if available or the polyvalent serum may be continued If the infecting organisms is found to belong to the other types against which no therapeutic sera are available the injections should be discontinued

Feltons serum is a concentrated serum containing antibodies against type I and type II pneumococcus

The use of such a serum reduces the temperature, pulse rate respiratory rate and the toxæmia The inflammatory change in the lungs is checked, but it has no influence either on the rate of resolution or on the complications

The intravenous route is the method of choice for the administration of the serum If there is any reaction it can be controlled by intramuscular or intravenous injection of 0.5 to 1 ccm of 1 in 1000 adrenalin solution The risk of allergic reaction following the first dose may be minimized by slowly giving 1 ccm of serum intravenously either pure or diluted with sterile normal saline The rest of the dose is given after an interval of 20 to 30 minutes

[illegible]

Antimeningococcus serum It has been used extensively in the treatment of cerebrospinal fever for a long time The earlier reports as to the efficacy of such a serum were somewhat exaggerated but the present day opinion is that the serum given early controls the infective process and shortens the illness The complications and sequelæ are much less relapses are also less frequent and the disease does not continue so long Although this is the usual experience with antimeningococcus serum there are some cases where this form of treatment fails entirely The reason for this is that the meningococcus consists of a heterogenous antigenic group and the serum to be effective must be prepared from a large number of representative strains from these different antigenic groups Further it has been seen that strains isolated from sporadic cases are different from the epidemic strains and sera prepared from such strains are of little therapeutic value in epidemics The best method therefore would be to collect a surplus stock of the serum during an epidemic period and to use it for the next epidemic till organisms are freshly isolated and fresh sera raised

There is no known method of titrating this serum The experiments of McKenzie and Martin have shown that substances bactericidal to the meningococcus are present in increasing amounts in the serum of acute and chronic cases of cerebrospinal fever and the serum of convalescents Encouraging results have been reported on efficacy of such a serum in the treatment of cerebrospinal fever but technical difficulties have hindered its trial on a large scale

Daily intrathecal injections of from 30 to 60 ccm for an adult and 10 to 20 ccm for infants have been found to give satisfactory results At least 4 doses in all should be given but there cannot be any hard and fast rule about the dosage since it depends on the severity of the illness and various other factors Two points should be noted in its

[illegible]

safeguard against relapse

As regards the route of administration the intrathecal route is the best but in predominantly bacteriæmic cases intramuscular injections of the serum may also be given in addition to the intrathecal injection The intracisternal route is recommended in cases of subarachnoid block and is widely practised in the United States It should not be undertaken by persons who have not had previous practice on cadavers

Anti anthrax serum Anthrax is primarily a disease of animals and man is attacked only when engaged in an occupation which brings him in contact with such infected animals or their products Of the three clinical forms of the disease the cutaneous type is the only one in which the administration of an antiserum is of some benefit Although many different types of sera have been prepared and used from time to time Sclavo's serum, which is perhaps the earliest preparation (1895), is the best

Sclavo's serum is given in doses of 30 to 40 ccm subcutaneously followed by a similar dose after 24 hours if the local lesion or the general state of the patient does not improve In severe cases 10 ccm should be given intravenously and repeated after 2 or 3 hours In addition subcutaneous doses should be given as well It should be noted that the best results are obtained by the administrations of the serum at the earliest possible moment

Antityphoid serum Although attempts have been made to use antityphoid serum in the prophylaxis and cure of typhoid fever the results have been very contradictory and the value of such treatment is extremely doubtful Gross (1930) prepared a necrotizing toxin from *Bact typhosum* and he used this toxin for immunizing horses The antitoxin so prepared is capable of producing both a prophylactic and curative action in mice Besides the antitoxin it also contains agglutinins complement fixing and bactericidal bodies Reports on the clinical use of such a serum are not encouraging

Antistaphylococcus serum
aureus may be associated with
at Bundaberg in Queensland ir
inoculated with a diphtheria pr(
become contaminated with staph

Puerperal infections caused by the staphylococcus have been treated with large daily doses (100 ccm) of this serum in Germany It should be used as a precautionary measure in cases of furuncles of the lip carbuncles puerperal infections The use of staphylococcal toxoid in the treatment of furunculosis has already been discussed in the section on vaccine therapy

in such wounds was extensively tried both for treatment and prophylaxis and has been found to be of great value particularly in prophylaxis Gas gangrene is not so commonly met with in civil practice but in the likelihood of a wound being infected with anærobic bacilli, a polyvalent antiserum should be injected as a prophylactic measure The serum given intravenously and injected into the deep tissues near the wound has been found to give satisfactory results and as much as 1 000 ccm may be required It is most important to treat wound surgically in addition to the serum treatment

This serum has also been used in acute abdominal conditions such as appendicitis and intestinal obstruction Williams recommends administration of 80 ccm of the serum intramuscularly and an additional 40 ccm intravenously in very severe cases of intestinal obstruction On subsequent days 40 to 80 ccm should be given intramuscularly until the distension has disappeared and the bowels are moving spontaneously and regularly A prophylactic dose before operation is advisable Its administration as an adjuvant to operative measures has proved to be of great benefit It has also been used in the treatment and prophylaxis of puerperal sepsis due to infection with these pathogenic anærobic ... entrated
... been
... The

(4) Antiviral Sera

Measles The cause of this disease is a filtrable virus which is present in the blood and nasopharyngeal secretions during the acute stage of the disease It has not been possible to obtain an antiserum by immunizing animals so that human convalescent serum is needed

for prophylaxis There are two types of protection —(a) Full but temporary protection, (b) incomplete protection resulting in a mild attack of the disease One attack of the disease confers a lasting immunity

in a poor state of health, particularly those
belo tuberculosis rickets diphtheria, whooping
coug of infection The immunity lasts for 3 4
weel that period

The effective dose for such a purpose depends on (1) the age of the child (2) the state of his health and (3) the interval between the time of exposure to the infection and the time when the serum is given this should not be more than five days The average minimum dose is 5 ccm and the dose for children over three years of age is determined by multiplying the age of the child by two and the result gives the number of c cm of serum to be administered The duration of the protection so conferred depends on the time of its administration If it is given before exposure the immunity lasts from 2 to 4 weeks but if given early in the incubation period some degree of active immunity may be superimposed upon the passive immunity and if this happens the patient will be protected for a few months

Convalescent serum normal adult human serum and whole adult blood are three different agents used for such protection. It is not always easy to obtain convalescent

[illegible] of the whole blood 25 to 50 ccm are needed to confer full protection

Owing to difficulty in obtaining sufficient quantity of serum use is now being made of human placental extract If the use of the placental extract proves successful it would be possible to immunise the children on a large scale

Incomplete protection or attenuation as it is called is obtained by first exposing the child to infection for example by letting him run about with a case of measles for a day or so and then giving him an attenuating dose The attenuating dose is the same as the dose for complete protection if given within 6-9 days after exposure or half that dose if given within 1—5 days after exposure Unless contra indicated by the weak health of the child it is much better to aim at attenuation rather than at complete protection because the mild attack of the disease will confer a lasting immunity Attempted attenuation is however difficult because one has to be sure that there has been an intimate and close contact with a case

Acute anterior poliomyelitis Human sera from three sources are used —(1) Convalescent serum (2) serum from persons who had an attack previously even up to 10 or 20 years (3) serum of normal adults with no history of having suffered from the disease There is evidence to show that sera of persons who have never suffered from poliomyelitis contains immune bodies probably as a result of an acquired immunity due to sub infective doses of the virus in childhood

From 10 to 20 ccm is given at the earliest possible moment intrathecally and this is followed immediately by a dose of from 40 to 200 ccm intravenously The intra thecal dose may be repeated on two or three successive days but there is no necessity for repeating the intravenous dose There is no danger in injecting human serum intravenously as it is rarely followed by unpleasant sequelæ It is no use giving the serum after paralysis has set in

Prophylactic inoculation can be done either by human antiviral serum or by immune serum from horses Flexner and Stewart (1928) suggest a subcutaneous dose of 10 ccm for children and 20 ccm for adults repeated after 4 or 6 weeks if exposed to infection

Chicken Pox Although a comparatively harmless disease prophylactic measures are justified due to the long incubation period necessitating a prolonged quarantine Convalescent serum has been used for this purpose

Mumps Convalescent serum has been used both for prophylaxis and alleviation of symptoms and complications of this disease The results so far obtained are encouraging but not convincing

Dengue Convalescent serum has no protective action when given prophylactically or in the treatment of the disease

Antivenin This is an antitoxic serum against snake venom and considering the large number of deaths occurring in India from snake bite, it should be one of the most useful antisera Unfortunately however there are so many practical difficulties in the preparation and use of this serum that it has not so far been very successful For details see chapter on snake venom

5. Bacteriophage Therapy

The discovery of bacteriophage is of comparatively recent date Twort (1915) in a paper entitled "Investigation on the nature of ultra microscopic viruses' first noted the existence of such an agent d Herelle, working at the Pasteur Institute, Paris discovered a curious phenomenon in sterile filtrates of stools of patients suffering from the Shiga type of dysentery The unique feature of this phenomenon, and one outside the realm of previous experience, was that the lysis produced by filtrates in cultures was transmissible in series *ad infinitum* without exhaustion of the lytic principle This lytic principle was named *Bacteriophagum intestinale* or *Protobios bacteriophagus* d Herelle (1917) considered the bacteriophage to be a minute, ultra microscopic, living organism parasitic upon, and lytic towards bacteria and he has since done considerable amount of work in support of this theory

Although bacteriophage as we now know it has been known for about thirty years, there are to be found indications of appreciations of its existence in the past Most discoveries have their roots in the past In certain parts of India the droppings of birds have been used for centuries past in the treatment of dysentery and other intestinal diseases, the use of cow dung spread on the floors of kitchens as a purifying agent, was at one time and still is in many if not all parts of India, a common routine in the households These practices were undoubtedly based on experience and clinical observations of many generations The droppings of birds have been shown to contain very powerful bacteriophages against the organisms of dysentery at times against the cholera vibrio and even the typhoid group of organisms The spreading of cow dung to 'purify' the kitchen floors, etc although now shrouded in the rituals of religion is an efficient though undoubtedly a very primitive form of disseminating bacteriophage The drinking of river waters the administration of certain waters to the sick would also appear to be a method of bacteriophage prophylaxis and bacteriophage therapy

Hankin (1896) drew attention to the purifying effects of the river water He noted the bactericidal properties of the waters of the Jumna At Agra, for instance be found that the river water contained 100,000 bacteria per ccm whereas 10 miles further down there were only 100 per ccm This observation remained unexplained till the discovery ... orkers also observed many peculiarities in cultures of intestinal ... e nibbled appearance and defective colonies ... nising their abnormality This we now know

(1) Nature of bacteriophage

Opinions differ regarding the nature of bacteriophage A controversy as to whether it is a living organism or a dead product of a living organism is still raging But the consensus of opinion tends to regard it as a living organism If we consider the size of bacteriophage it will be appreciated how very difficult it is to settle the question of the nature of such an object Bacteriophage is ultra microscopic *i e* not visible by the most powerful microscope Recent studies show that phage is composed of particles whose size is uniform for any phage though varying from phage to phage The smallest phage has a diameter of 8 to 12 , while that of the largest phage varies between 50 to 75

... living strictly parasitic ... tiplies at the expense of ... is but one bacteriophage ... n the name of *Protobios*

derived from the chromosomes Bordet and Ciuca (1921) consider that the phenomenon of bacteriophage is due to an inherited autolytic power on the part of bacteria Hadley (1928) is of opinion that bacteriophage as it occurs is a definite stage in the life cycle of all bacteria or that it is an essential constituent accessory to the various stages Otto and Munter (1924) state that it is a ferment like action of the colloidal particles of bacterial cytoplasm

Phenomenon of bacteriophagy lysis and mutation of bacteria

studied in the case of cholera ra contains phage and if a id culture of cholera vibrios ibrios being dissolved Under It consists of swelling and spherulation of the organism production of granules and finally disintegration of the bacteria The clear liquid can again be inoculated into a fresh culture to obtain the same effect and the process can be repeated indefinitely This illustrates the important characters of lysis of bacteria by bacteriophage *i e* its filterability transmissibility and that it can be subcultured in series with living and growing bacteria.

The phage action can be observed in young bouillon cultures of the cholera vibrio as well as in other media If an agar plate is thickly inoculated with culture of cholera vibrio so as to give a confluent growth and a few drops of a suitable dilution of the phage containing filtrate is spread over this inoculated surface before the plate is inoculated there will appear a number of well separated clear more or less circular areas within which there has been no growth These areas are generally called plaques These are the colonies of bacteriophage They vary in size from that of a pin head up to 4 to 5 mm small sized phages give rise to large plaques and large sized phages to small plaques

If the plates with their areas of plaques are further incubated it is found that after a certain time small colonies develop in these areas A similar phenomenon in the form of return of turbidity is observed in bouillon cultures rendered clear by phage The explanation is that after a certain time secondary colonies of bacterial cultures develop which consist of strains of bacteria resistant to the action of phage

The ...

can be realised from the fact that on it depends to a great extent the success or failure of the struggle that is going on between bacteria and the defensive mechanism of the host

Bacteriophage is one of the most powerful agents in bringing about changes in the morphology cultural and serological reaction of bacteria These reactions are known as mutation and dissociation of bacteria and consist in alteration of motility and morphology ...

The modification of bacteria in this way may be so complete that secondary cultures from the original strain may be morphologically quite different D Herelle described extremely resistant and stable forms of cocci obtained by repeated transfers of young secondary cultures of dysentery typhoid paratyphoid coli and cholera organisms Hoder (1925) stated that there is definite possibility of transition of *Bact coli* to paratyphoid like forms Doorenbos (1932) claimed the El Tor vibrio as a phage-modified form of cholera vibrio

The conversion of non hæmolytic organisms to hæmolytic forms of agglutinating to non agglutinating species by the action of bacteriophage has been described by many workers In the case of cholera Pasricha and his co-workers (1931) state that there is some bacteriophage as well as serological relationship between the true cholera vibrio and the cholera like forms Many of these latter forms are considered to be only mutation forms of the true cholera vibrio and play great part in the incidence of cholera Morrison (1931) on the other hand concludes from his experiments that the alterations in the cholera vibrio are due probably to the occurrence of bacterial contamination

Specificity and types of bacteriophage Burnett (1933) stated that bacteriophages are independent micro organisms and differ widely in size and activity d Herelle considers that there is only one species of phage but that it is capable of a high degree of adaptation to pathogenic organisms There may be races of phage with a specific affinity for a certain strain or a species of bacteria to the exclusion of all other strains of the same species which procedure has been regarded as a valuable aid to the diagnosis of bacterial species

Several types of bacteriophage have been recognised especially with regard to cholera phage This is dependent upon the fact that with the development of a resistant series of bacteria on culture a bacteriophage may be discovered which lyses these resistant strains. In this way several types of cholera phage have been recognised In India Asheshov called his types A B and C Pasricha and his co workers (1932) have added types D E and F to these already known ones

(2) Preparation of bacteriophage

The technique of bacteriophage study and the general principles of bacteriophage are so highly specialised that they involve special methods and what first appears to be a highly complicated technique In reality it is perhaps one of the simplest techniques in the whole subject of bacteriology It must be remembered that we are dealing with an organism which is so small in size that it passes filters which hold back all microscopically visible forms of life This extreme minuteness of the bacteriophage corpuscle is of very definite advantage because it makes it possible for the bacteriophage to be separated from all visible forms of life by the simple process of filtration Bacteriophage also possesses an additional property which is of extreme value in its preparation and study It can only grow and multiply at the expence of living susceptible bacteria Its food is the living bacteria and so far it has not been possible to devise any method for its propagation except on living material and those of its host

Technique of filtration This varies according to the nature of the fluid required to be filtered It is generally done in the following way Sterilised funnels with filter paper are filled with kieselguhr suspension This leaves a very thin coating of kieselguhr on the filter paper which retains most of the bacteria giving an almost crystal clear solution. This clear filtrate is now filtered through porcelain candles under vacuum of 15 inches

Isolation of bacteriophage In order to isolate bacteriophage from stools, about 5 ccm of the stool if liquid or a small portion if so
(papain broth or any other liquid medium)
is minimal a few ccm of young peptone w
bacteriophage is sought are added The addi
of giving the bacteriophage present the opportunity to develop and thus to be more readily found

Isolation of bacteriophage from water is done by following the same procedure Large amounts of water may be necessary and often preliminary filtration is required before the addition of enriching organisms'

(3) Role of bacteriophage

The phenomenon of death recovery and immunity from diseases has been explained on the basis of development or absence of bacteriophage d Herelle believes that such a phenomenon is not dependent upon immunity, as is generally understood but on the occurrence of bacteriophage In the case of cholera
cases v ge
which er
prompt er
with some delay and the ups and downs in the clinical progress of the case represent the behaviour of the bacteriophage Bacteriophage by infecting bacteria causes destruction and death of bacteria and is the direct agency of recovery of disease in man By an indirect process it brings about a state of acquired immunity Bacteriophage by causing a solution of the bacteria presents the bacteria in a condition to serve as ideal antigens The lysates contain the lysed bodies of bacteria and induce in the body the mobilisation of the defensive forces

If, however, the bacteriophage is not powerful enough or conditions are not suitable for the total destruction of the invading bacteria, then one of the two things may occur —

(1) The bacteria may overcome the infection by bacteriophage and develop an immunity against that particular bacteriophage and persist as saprophytes in this condition they are entirely non pathogenic The question now arises whether these bacteria under any circumstances again become virulent and pathogenic There is no direct evidence to either admit of this possibility or to define the conditions necessary for such changes to occur It appears to be highly probable however that such changes do occur in nature and it is only rational to conceive that such changes should be the rule rather than the exception

(2) The bacteria may be able to completely rid themselves of the infection by bacterio phage, and although they develop an immunity against that particular phage they lead a life in harmony with bacteriophage There is a symbiosis between the causative organism and bacteriophage and this results in attenuation of the virulence of the bacterium such bacteria cause chronic disease Acute diseases are due to young healthy disease free or bacteriophage free bacteria, chronic diseased conditions are caused by the diseased unhealthy phage infected bacteria which inspite of their disability yet retain sufficient invasive power to maintain a chronic diseased condition

Such is the line of reasoning which has been advanced but from the very nature and number of variable factors present the proof of such conditions actually occurring is not very convincing *Bact typhosum* in its active pure stage causes typhoid fever provided certain conditions exist under which it can exert its full invasive power but *Bact typhosum* contaminated with bacteriophage—the organism of the carrier state—may only cause a chornic infection such as cholecystitis *V cholerœ* when pure and healthy kills a high percentage the mortality rate is low or may cause very mild symptoms when infected with phage *Past pestis* kills rats when free but when diseased it causes only a chronic form of plague The theory of bacteriophage can even embrace complete consistent theory of acquired immunity but these ideas should not be stretched too far in our present stage of knowledge

(4) Bacteriophage in prophylaxis and treatment of disease

d Herelle has shown a very definite relationship between the occurrence of bacteriophage in nature and the incidence of certain intestinal diseases particularly cholera and dysentery At the beginning of the cholera season very few samples of waters collected from the river Hooghly and from the tanks in Calcutta show the presence of choleraphage During the height of the cholera season the incidence of bacteriophage in nature increases till about 40 to 50 per cent of the samples of water show the presence of powerful choleraphages At the end of an epidemic, the whole bacteriological picture changes instead of the cholera vibrio possessing typical characters which may be likened to a well organised army, there are towards the end of an epidemic heterogenous [illegible]

vibrio and phage for dominance, and the ups and downs of all epidemics are the visible effects of that stupendous invisble battle that takes place in nature The battle ground is the intestine of man

This concept of prophylaxis and immunity is so radically opposed to our ideas of epidemiology that at present it is difficult to appreciate its importance It must be realised now that there exist in nature two very distinct forces—one certain bacteria which are harmful to man and that source of these harmful bacteria in the majority of instances is man himself, the other, another living force which because it is harmful to bacteria is of distinct value to man This second

force is as it were provided by nature to maintain a state of equilibrium between man and his bacterial enemies It is a police force provided by nature to guard mankind in times of stress If conditions are favourable this force of bacteriophage multiplies so readily and becomes so powerful that it brings to an end the supremacy of the bacteria

These theories raises very important points both in the prophylaxis and treatment of epidemic diseases From this point of view the question arises whether the propagation of bacteriophage is advisable To do this are we to allow the unhampered dissemination of natural bacteriophage which would necessitate the cessation of all public health activities and to rely entirely on the results of the natural adjustment between the bacteria and the bacteriophage? These last factors may be so variable that it would not be justifiable to allow the cessation of the stringent sanitary measures The bacteriophage as it exists in nature has had centuries of free play unhampered by any sanitary measures and we still have big epidemics of intestinal diseases Secondly the bacteriophage as they exist in nature may be supplemented by specially trained and highly virulent bacteriophages In this way it may be possible to marshal together the natural enemies of bacteria and harness nature for the benefit of mankind. This certainly must appeal to everyone as the most rational point of view Experiments in the laboratory and trials with bacteriophage in the field both as a prophylactic and therapeutic agent have been undertaken by several workers and although bacteriophage prophylaxis and therapy have made great progress the subject is still under trial and no definite conclusions can be drawn from the experiments reported so far

It can be definitely stated that the results of the trials so far are not against bacteriophage there is evidence highly suggestive that bacteriophage is of value Though great hopes were raised at first of the therapeutic value of bacteriophage the results so far have not fulfilled these hopes Great things are still expected from bacteriophage which on purely theoretical grounds possesses all the attributes of an ideal antiseptic It has no action whatsoever on any living tissue kills the invading organism rapidly and increases in amount as it does so The conditions within the body may and do modify the effectiveness of its attack but it is hard to believe that an active phage can be entirely without effect on the course of an infection by a sensitive organism

Therapeutic uses As early as 1921 bacillary dysentery was treated by administration of bacteriophage and since that time various results were obtained with this form of therapy

According to d Herelle in the bacteriophage there is a natural therapeutic agent which is of value in the cure of disease as well as in prophylaxis It has already been pointed out that an active specific phage possesses all the attributes of an antiseptic and it kills the specific organism against which it is employed and increases in amount during this process From this point of view it was considered a valuable therapeutic agent in bacillary dysentery cholera and various other bacterial diseases Unfortunately the success with bacteriophage treatment is not uniform and its usefulness has been disputed by many workers It is said that the action of bacteriophage is brought about by purely chemical means and that the effects produced are nothing but a reaction due to the introduction of a foreign protein Topley Wilson and Lewis (1925) used bacteriophage in strictly controlled experiments with mouse typhoid infection Their observations were that the presence of bacteriophage does not prevent the spread of infection

check an epidemic when it once started or appreciably reduce the mortality. They further found that there is no evidence of development of immediate immunity either from injection or ingestion of bacteriophage.

Recently however, Asheshov, Wilson and Topley (1937) using a phage active against vi strains of *Bact. typhosum* have shown in their experiments on mice that a phage may be active *in vivo* as well as *in vitro*. They are of opinion that under suitable condition, a phage that has a specific action on the surface antigen of a virulent bacterium is capable of exerting a significant protective action when it meets that bacterium in the tissues.

The majority of those who are however willing to accept d'Herelle's hypothesis are of opinion that bacteriophage is a living ultramicroscopic virus which is capable of being a parasite on bacteria and which is said to dissolve and destroy them through the agency of a ferment it secretes. In addition to its direct action on bacteria, bacteriophage may also exert an indirect action by increasing the phagocytic power of the leucocytes, the explanation being that [illegible]

The bacterial split products obtained under the action of bacteriophage are in a physical state highly suitable to induce a strong and durable immunity so that this immunity adds indirectly to the value of bacteriophage as a therapeutic agent.

According to d'Herelle many of the unsuccessful results of bacteriophage therapy are due to the inadequate technique in the preparation of phage. Only the potent phages are therepeutically effective.

The role of bacteriophage as a therapeutic agent is as yet complex. Satisfactory results can only be obtained by following certain procedures. It is to be understood that there is an essential difference in principle between the treatment of acute and chronic infectious diseases with bacteriophage. In cases of acute disease a powerful bacteriophage must be brought into contact with the pathogenic bacteria before they have had opportunity to produce sufficient lesions to cause death. Chronic cases possess a different aspect altogether from the point of view of bacteriophage treatment. In this condition a state of partial symbiosis exists between the infecting bacteria and the phage and in order to bring about a full therapeutic effect a race of bacteriophage has to be employed which is virulent for the bacteria.

The mode of administration and dosage of bacteriophage requires some consideration. Bacteriophage to be of any value should be administered as early in the course of the diseases as possible. Bacteriophage must come into direct contact with the invading organism and hence in intestinal disorders it should be given by the mouth. In cases of infection of the urogenital tract bacteriophage has to be introduced directly into the bladder, localised infections of subcutaneous or deep tissues required the direct application of bacteriophage in the infected focus. With regard to dosage and frequency of treatment it may be stated that the amount of bacteriophage to be given depends upon the virulence of the bacteriophage employed. This is due to the fact that bacteriophage in the presence of susceptible organisms perpetuates itself and the amount administered does not determine the amount that will ultimately develop. In case of acute infections a few administrations may be sufficient while in chronic types of infection bacteriophage therapy may have to be continued over a long period.

Bacillary dysentery The treatment of bacillary dysentery with bacteriophage is now widely recognised Fletcher tried bacteriophage in 22 cases of Flexner infection, but the treatment was a failure while in the Shiga type of infection the bacilli disappeared from the stool on the second day of the disease. Morison however obtained encouraging results in an epidemic of dysentery 70 cases were treated with 2 ccm of bacteriophage three times daily and of these three died and *the rest were all cured* The author has treated a large number of cases of both acute and chronic dysentery with bacteriophage with indefinite results In a few cases the effect produced appeared to be marvellous but in the majority of cases no improvement could be detected The results of trials by various observers, appear to indicate that bacteriophage therapy in dysentery is worthy of further trial

Cholera Bacteriophage therapy in cholera has been advocated In this connection it is worthy of note that the therapeutic phage employed in the treatment of cholera must be virulent The existence of a case with virulent bacteriophage should therefore draw special attention Along with this must be considered the vibrios *some may yield to a* phage of higher virulence while others may lead to actual diminution in the virulence of the bacteriophage In order to obviate this difficulty Asheshov recommends a method of keeping therapeutic phage virulent by repeated cultivation on a freshly isolated vibrio

The results published by d Herelle and others (1930) who investigated the problem of bacteriophage on behalf of the Government of India appear to be striking enough In a total of 198 cases of cholera 74 received bacteriophage treatment of whom only 6 died while in a series of 124 cases not receiving the phage treatment the mortality rate was 58 per cent *In Brazil* as a result of controlled experiments conducted by da Costa Cruz (1923) the Brazilian Government have distributed bacteriophage for the treatment of bacillary dysentery This mode of treatment quickly supplanted all others including the use of anti dysentery serum which has been abondoned In Calcutta dysenteryphage is being widely used deMonte (1938) recorded the reports received from physicians who treated 90 cases with bacteriophage active against the important dysentery strains Seventy six of these ninety cases were dysentery and good results were reported in 61 or 80 per cent eight were diarrhœas and all recovered and six were colitis of which one benefitted. The dysentery phage was prepared in the School of Tropical Medicine and supplied in 2-3 ccm ampoules The contents of one ampoule were taken in a wine glass of drinking water immediately after a dose of a mixture containing 60 grains of sodium sulphate and 10 grains of sodium bicarbonate The number of doses administered varied severe cases were given a dose every two hours up to six doses a day mild and recovering cases one dose

is uncertain and usually unsatisfactory

In cholera Morison and Vardon (1929) used a combined dysentery-cholera phage in two epidemics of cholera in Assam A mortality of 75 8 per cent resulted in cases having no bacteriophage while the death rate was 29 0 per cent in cases receiving bacteriophage treatment They mostly employed 2 ccm of phage four times daily by the mouth and serious cases received 2 ccm along with hypertonic saline Asheshov (1931) treating cases claimed almost 100 per cent success Souchard (1930) on the other hand failed to obtain any benefit and in his series a mortality of 24 out of 27 resulted Others too obtained disappointing results In a series 57 per cent died in the phage treated series whereas 53 per cent died in the control series

More recently Pasricha deMonte and O Flynn (1936) in a carefully controlled experiment treated 398 bacteriologically proven cases of cholera with choleraphage and compared the results obtained with that obtained in 443 similar but alternate cases not given cholera phage but which in other respects received identical treatment The case mortality in the phage treated groups was 8 3 per cent as against 17 8 per cent in the control series Again Pasricha deMonte and others (1939) conducted a comparative trial in which the results of treatment by five different methods (calomel potassium permanganate essential oils choleraphage and M & B 693) were compared Altogether 244 cases were treated and the results showed that cholera phage gave the best therapeutic results Indeed these workers suggest that the result of choleraphage therapy are so encouraging as to justify the adoption of bacteriophage as a routine measure in the treatment of cholera. They administered choleraphage orally about 2 ccm three to six times a day according to the acuteness of the attack in addition to hypertonic salines

Enteric fever Contrary to the favourable results obtained with bacteriophage therapy in the infections of the intestinal canal such as dysentery and cholera its efficacy in enteric fever is doubtful Some clinicians have reported excellent results Strains of phage virulent

to the organism *in vitro* under laboratory cond tions have been obtained but these may be entirely ineffective in actual treatment of the disease There are however occasional favourable reports with bacteriophage treatment The usual dosage in such cases in 2 ccm of the phage three t mes daily for four to five days Intravenous injections of the phage have been resorted to to lower the temperature and hasten recovery In view of these results and of the diverse reports that have been published regarding bacteriophage therapy in typhoid and paratyphoid fevers the question of appl cation of bacteriophage in the treatment of this disease stil remains unsettled

Plague The treatment of plague by bacteriophage has not as yet been carried out on a large scale and its value is therefore still undetermined d Herelle reported successful

had l ttle success with a strain of powerful bacteriophage in l uman or in animal plague Experiments on mice carried out in the Haffkine s Institute have shown that bacteriophage has no protective or curative effect in infect on with *Past pestis*

Pyogenic infections Certain favourable results are also reported in localised septic conditions due to staphylococci and streptococci Furunculosis carbuncles, abscesses osteomyelitis and miscellaneous infections have been treated by this method The usual procedure of application of
injection although a few
application of bacteriophage
of which may vary from 0
to 48 hours In the cases
have given very encouraging
phage in most acute urina
suppurative conditions and found it satisfactory

to aspirate such pus as may be present in it before injecting the phage

Summary—About thirty years ago a curious phenomenon was first observed in laboratory cultures of bacteria. It was noted that in agar plates which had been thickly sown with colonies of staphylococci clear areas which were found to be free of bacteria had appeared It was also observed that at a particular stage in the growth of certain cultures of the dysentery bacillus the entire culture would suddenly clear up and become free of bacteria D'Herelle named the agent responsible for this phenomenon 'bacteriophage

It was surmised that if
ration which when administe
in the human body, it woul
Intensive studies were, ther
Bacteriologists and physicians cherished the hope of utilizing bacteriophage in the prophylaxis and treatment of diseases of bacterial origin

Preparations of bacteriophage.—For therapeutic use bacteriophage is available in liquid form It consists of a filtrate of broth cultures of bacteria which have been dissolved by the addition of bacteriophage. This filtrate, or lysate is used locally as a wet dressing or may be injected subcutaneously intravenously or intraperitoneally to combat bacterial infections It has also been given by mouth when its action is desired in the intestines but unfortunately both gastric juice and bile have an inactivating effect on bacteriophage When it is administered with sodium bicarbonate on an empty stomach however, less seems to be destroyed and appreciable amounts get through into the intestine Bacteriophage has also been administred in form of retention enemas For local application the filtrate has been combined with a water soluble jelly base to form a gel preparation

Since each germ or at least each group of related germs is believed to produce a bacteriophage peculiar to itself, there are several filtrate preparations and several gel preparations Bacteria from which these are made include the streptococcus staphylococcus *E coli V cholerae* and such invaders of the respiratory tract as the pneumococcus *N catarrhalis*, etc Frequently two or more types of bacteria are combined in one preparation

Nature of bacteriophage.—D Herelle thought that the causative agent was a living substance too small to be seen by the most powerful microscopes The bacteriophage was considered to be parasitic on bacteria which it destroyed in the process of reproducing itself, in fact it was an ultra microscopic parasite on a microscopic parasite

Opposed to this view is the belief that bacteriophage is a by product of the metabolism of the bacteria themselves According to this concept the staphylococci or dysentery germs produce a substance which is toxic to the germs themselves The effect produced by bacteriophage is from this view point an autointoxication and there is no question of its being an external organism of parasitic nature

This latter view has been strengthened by recent studies on the behaviour and chemical nature of bacteriophage Chemically bacteriophage has been shown to be a protein of high molecular weight It forms only when conditions are favourable for the growth of bacteria and the better the bacteria grow the faster is the bacteriophage produced Under ideal laboratory conditions the following sequel of events takes place bacteria multiply rapidly and continuously bacteriophage begins to form and increases in quantity a point is reached where enough bacteriophage has been produced to lyse all of bacteria present and this is rapidly accomplished

The question arises why the phage does not form in the body when bacteria have invaded the body and are freely multiplying thus freeing the body of the

bacteria seen so rapidly in test tubes where no serum or tissue is present is prevented in the body

Mode of action of phage in vivo.—In spite of its inactivation within the body there are some situations in which bacteriophage may be of value and attempts have been made to learn how it produces its action in the body Four possible ways have been suggested to explain the mechanism of phage activity in the body and at least three of these are of unquestionable importance

Firstly, bacteriophage stimulates the activity of phagocytic cells of the blood and tissues These "scavenger cells" are of tremendous importance in freeing the body of certain kinds of germs, and their activity in the presence of large amounts of bacteriophage is considerably increased and they are thus enabled to engulf and destroy the bacteria For example in the case of boils, the scavenger cells' engulf tremendous numbers of the infecting bacteria and the use of the appropriate phage gel locally on the boil to stimulate this activity is beneficial

Secondly, when bacteria are dissolved by phage in the body the components of the lysed bacteria act as antigens to stimulate the formation of antibodies These antig nic actions are greater than those of undissolved bacteria and so indirectly phage increases immunity to the diseases and acts as a vaccine When the bacteriophage is administered as a biologic preparation the benefit actually comes from the bacterial parts that have been liberated when phage was added to the bacterial culture

Thirdly, phage preparations may activate non specific mechanisms of immunity in the body, comparable to those stimulated by other non-specific vaccines In certain cases a non related substance may promote immunity to attack from a particular germ and there is sufficient evidence to indicate that phage lysates may sometimes act in this fashion

Fourthly, it is possible, but not very probable that phage may affect growth of bacteria in the body in such a way that less virulent forms develop

Value in therapy—Had it not been for spectacular development of the sulphonamides and antibiotics bacteriophage therapy might be in greater use today than it actually is Some observers have obtained good results in the prevention and treatment of cholera with bacteriophage preparations Properly prepared lysate can be useful as a vaccine for certain infections caused by staphylococcus such as boils as an agent to induce non specific protein shock in certain diseases such as typhoid fever and as a local agent to stimulate the activity of the "scavenger cells in a locally infected area Many promising possibilities were anticipated With the chemotherapeutic and antibiotic agents now available phage therapy has been relegated to the background It is possible that further research may show that phage has a definite place in the treatment of bacterial diseases

therapeutic effect could be obtained in infected *animals* *Further work led t* the discovery of azo compounds with marked bactericidal properties *in vitr* but no action *in vivo* in the mouse Later studies confined to compounc containing the sulphonamide group and tested only *by animal experiments* le to the discovery of drugs effective against streptococcus infections in animal In 1932 a patent was obtained for the azo dye sulphonamide crysoidin whic was found by Domagk (1935) to cure an otherwise fatal streptococcus infectio in mice This compound which was very sparingly soluble was placed on th market under the trade name of "Prontosil (Prontosil rubrum) and secure for Domagk the Nobel Prize A more soluble compound for intramuscula injection was described shortly afterwards and was called 'Prontosil soluble or Neoprontosil' In France a similar compound named "Rubiazol' wa prepared in 1935 and the experimental work of Domagk was confirmed It was als shown (1936) that in the tissues of the host the azo dyes were split at th azo linkage and that prontosil yielded para amino benzene sulphonamide whic was thought to be the chemotherapeutic portion of the molecule This compoun was prepared by Fourneau and it was shown that it was as effective in curin experimental infections as was prontosil

Even before the appearance of Domagk's paper in 1935, mention of th treatment with "Streptozon" (Prontosil) of patients with infections appeared in German clinical journals and afterwards numerous favourable results in human infections were reported *It was only, however, after the publication of the* paper on the marked beneficial effect of prontosil in puerperal sepsis that con siderable interest was awakened in the English speaking countries with regard to these compounds

Buttle and others took up the work and confirmed the findings that para amino benzene sulphonamide was effective in haemolytic streptococcal infections *in mice, and also cured meningococcal infections Work was also started in* the U S A which confirmed the previous work with regard to para amino benzene sulphonamide and further basic contributions were made with regard *to its pharmacology and toxicology* The name of sulphanilamide was given to this compound by the Council of Pharmacy and Chemistry of the American Medical Association This work led to the extension of use of sulphanilamide in the chemotherapy of infections other than those with hæmolytic streptococci A large number of derivatives of sulphanilamide were developed and tested for their clinical value not only in bacterial infections but also in protozoal and virus infections Some of these compounds are benzyl sulphanilamide (septazine), di sulphanilamide (disulon) and its dimethyl derivative (uleron) The best of these compounds was sulphapyridine (M & B 693) synthesized in England

Newer compounds—Whitby (1938) working with sulphapyridine on mice inoculated with pneumococci and with haemolytic streptococci, found that it appeared to exert an action on the capsule of the pneumococcus and that it was as active as sulphanilamide against a haemolytic streptococci and meningococci Many new compounds were produced and a flood of communications on the subject has been appearing ever since Further work has greatly clarified the views on the whole of this group of drugs

Sulphathiazole and sulphamethylthiazole were introduced in 1939 with high *hopes for activity against staphylococcal, pneumococcal* and other infections and encouraging results were also obtained against plague in India New compounds such as sulphanilyguanidine or sulphaguanidine, sulphadiazine, sulphamerazine, etc , have been prepared which are more effective and less toxic Sulphaguanidine

is little absorbed from the gastro intestinal tract and has given good results in acute bacillary dysentery and cholera and sulphadiazine and sulphamerazine are reported to be less toxic than sulphathiazole and sulphapyridine Many new uses and methods for application of these compounds are developing particularly in surgery

During recent years the number of sulphonamide compounds have rapidly multiplied and are being tried in all sorts of conditions and diseases War Memorandum No 10 of Medical Research Council of England summarised the position with regard to this group of compounds for the benefit and guidance of Military Medical Officers and has been freely utilised in the preparation of this section

Although these compounds have been recently overshadowed by the rapidly developing group of antibiotics there is no doubt that their reliability in the treatment of many infections is still great Their proper use however, needs a thorough comprehension of their pharmacological action therapeutic application and toxic effects These have therefore been dealt with in detail

2. Chemistry and nomenclature

Term Sulphonamide—On account of their complicated chemical structure and partly because of the confusion that has resulted from the variety of trade names used by

septicaemia in ... This compound is an azo dye which liberates sulphanilamide in the body to which most of the activity is attributed. Sulphanilamide (para amino-benzene sulphonamide) itself is the simplest of the sulphonamides and is the mother substance of the other derivatives This substance has been known to organic chemists for nearly 40 years is soluble in water colourless and comparatively slightly toxic for mammals It is the therapeutically active principle of the azo compounds and sulphanilamide and its derivatives have largely replaced them in therapy

All these compounds contain at least one benzene group C_6H_6 ⬡ at least one amino group (NH_2) and at least one sulphonamide group (NH_2SO_2) If we start with benzene and add amino group (NH_2) to it we obtain amino-benzene ⬡ $-NH_2$ which is the chemical name for well known substance aniline By attaching a sulphonamide group to the amino benzene in the para position we obtain para aminobenzene sulphonamide

NH_2SO_2- ⬡ $-NH_2$ or aniline sulphonamide which has been abbreviated to sulphanilamide and so the simplest of all such compounds is formed The entire series of these remedies is known as the sulphonamides because they contain the sulphonamide group *viz* $-SO_2NH_2$

Two classes are recognized —

readily soluble in water

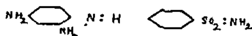
Nomenclature—Buttle (1939) has published a simple classification of the drugs now in general use based on the fact that sulphanilamide consists of a benzene ring to the opposite ends of which are attached an amino and a sulphonamide group The derivatives of sulphanilamide can be divided into two groups —those in which *the substituents are* introduced into the amino group, and those in which the substituents are introduced into the sulphonamide or amido group

mide, preparation 5214 and others

Group B—The second group includes sulphapyridine, sulphathiazole sulphadiazine sulphamezathine, sulphaguanidine, etc. In these the amido group is substituted by other groups such as pyridine, thiazole, guanidine etc

3. Sulphonamide drugs

(1) *Sulphonamido-crysoidin,* 4 sulphonamide 2' 4'-diaminoazobenzene ('Prontosil red, 'Prontosil rubrum or flavum'),



Almost insoluble in water, readily soluble in acetone This was the first sulphonamide compound to be used in therapeutics It is an azo-dye and in the body it liberates sulphanilamide to which its activity is due It is now replaced by the latter drug

Azosulphamide ("Bayer 102", Prontosil S or II, "Neoprontosil', Rubiazol injectible) is a soluble derivative

(2) Sulphanilamide (B P ,U S P) p aminobenzene sulphonamide



Solubility in water, at 15 50°C, 1 in 250, at 20°C, 1 in 170, at 25°C 1 in 115 More *soluble in presence of alkali* but no sodium compound is available in solid form Soluble in acetone sparingly soluble or insoluble in other common organic solvents Melting points 164 5 165 5°C.

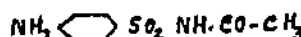
... absorbed from the gut and with the dosage usually employed, ... ncentration of 5 mgm ... ely severe infections ... xtensive burns is also quite rapid but in the case of wounds absorption is slower and irregular and in these cases *if there is co-existing systemic infection,* local applications of the drug require to be supplemented by oral therapy The drug may also be administered by the intravenous or subcutaneous routes in the form of a 0 8 per cent solution in saline or glucose The rectal route may also be used but twice the oral dose is necessary to maintain adequate blood con
to
of
10 to 15 per cent is acetylated so that nearly all is in active form ... the dose administered by mouth is excreted in urine, 2 to 3 days being required for complete elimination *of the drug after it is discontinued*

... and excreted entirely by glomerular ... The amount excreted thus varies ... a wound only about half appears ... m the wound

The toxicity of the drug is not high, agranulocytosis is rare, but acute haemolytic anaemia and acidosis are peculiar to this drug Nausea, vomiting headache and drug fever commonly occur *and drug eruptions on parts expo* to light are not uncommon Renal complications practically never occur Necr rarely occurs and it may be fatal

Sulphanilamide is particularly suited for local application because on account of its solubility and diffusibility no concretions form It is often combined with sulphathiazole to prolong its local action For systemic use the drug is not suited on account of its low potency

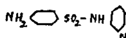
(3) *Sulphacetamide (B.P.C.)*, p amino benzene sulphonacetamide ("Albucid' 'Sulphacetamide')



Solubility in water, at 20°C, 1 in 150 Soluble in alcohol and in acetone insoluble in ether Melting point 181-184°C

1 in 1 5, sparingly
um salts of most
im sulphacetamide
ation of the com-
sues, such as the
conjunctiva

(4) *Sulphapyridine (B.P.C., U.S.P.)* 2· p-amino benzensulphonamido pyridine ("M & B 693', 'Dagenan").



Solubility in water is low, at 20°C, 1 in 3 000, at 100°C, 1 in 100 Soluble in alcohol and in acetone Melting point, 191-193°C Sodium compound solubility in water, at 15 5°C, about 1 in 3 in alcohol at 15 5°C about 1 in 20

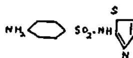
Absorption rate is slower than that of sulphanilamide and is erratic, after a single dose maximum concentration is not reached till after 5 to 6 hours For infections of average intensity, an initial dose of 4 gm followed by 1 gm every 4 hours maintains an average blood level of 5 mgm per cent The sodium salt is readily soluble and is used

In plasma much of the drug occurs in conjugated form, only 10 per cent is combined with plasma protein. Concentration in red cells is 60 per cent of that in plasma The

ecially
itients

appears in urine and more than 50 per cent in acetylated form, which has low solubility (11-89 mgm per cent) at pH of urine (5·4 to 8·2) Excretion is not completed even in 72 hours. Amount occurring in the fæces is variable but may be 20 per cent or more of the amount taken

(5) *Sulphathiazole* (B P C U S P) -2-p aminobenzenesulphonamide thiazole (Ciba 3714 or 'Cibazol', 'M & B 760' Thiazamide Eleudron)



Solubility in water, at 15 5°C, about 1 in 2,500 is greater than sulphapyridine, 96 mgm per cent in water and 250 mgm per cent in serum and 190-900 mgm per cent in urine Slightly soluble in alcohol Melting point 200 to 203°C Sodium compound solubility in water, at 15 5°C, about 1 in 3, in alcohol, at 15 5°C, about 1 in 20

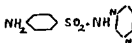
Sulphathiazole has probably the most potent bacteriostatic action of all the sulphonamide compounds its sulphanilamide equivalent being 50 and its bacteriostatic constant 1/53 for *Staph aureus* It is rapidly absorbed from the gut, and the blood level reaches its maximum in 1 to 4 hours after a single dose To maintain a blood level of 5 mgm per ... lium salt ... a 1 per ... 7 mgm

The toxicity of sulphathiazole is considerably less than that of sulphapyridine nausea vomiting and cyanosis being common Drug fever accompanied sometimes by enlargement of spleen and lymph glands and rashes are common especially after the seventh day of ...

... have to recur ...

Due to its great bacteriostatic powers, this drug is indicated in all severe infections It may also be used in infections with organisms of low drug sensitivity The drug is however, toxic and should only be used when less toxic drugs will not serve the purpose It is contraindicated in cases with dehydration and diminished urine secretion It has been found very useful in local applications to wounds in powder or micro-crystalline form on account of its solubility and slow absorption

... de pyrimidine (Pyrimal) It has a ... r at 25°C about 1 in 13 000 (15 mgm ... e In serum solubility is 160 mgm per ... Melting point 252 256°C Sodium com ... pH of 9 2 sparingly soluble in alcohol



Sulphadiazine is a less powerful bacteriostatic drug than sulphathiazole It is slowly but completely absorbed from the gut maximum blood concentrations being reached in 3 to 36 hours but usually within 6 hours Generally blood levels of 10 mgm per cent are required to be maintained and are achieved by an initial dose of 4 gm followed by ...

Sulphadiazine has a low renal clearance and this enables high blood concentrations to be easily maintained High concentrations in blood are obtained in moderate renal impairment and if these do not exceed 20 mgm per cent no harm results usually this should not exceed 15 mgm per cent The drug is acetylated in the plasma to the extent of ... han other sulphonamides At the normal ... per cent of the drug is bound to protein ... and body fluids In the cerebro spinal ... t in the blood

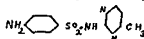
Only about 65 per cent of the intake is excreted in urine in 3 to 4 days and about

concurrently The low toxicity of the drug makes it the drug of choice for all moderate and mild infections and for prophylactic use in ambulant patients The drug is contra indicated in all cases with any degree of renal impairment

The drug is suitable for local application especially to corneal ulcers, burns etc, but on account of its low solubility it is dissolved in 8 per cent triethanolamine as a 2 5 per cent solution

It is suitable for use against all infections with sulphonamide susceptible organisms and in similar doses is more effective than sulphathiazole

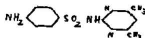
(7) *Sulphamerazine* 2-sulphonamido-4 methylpyrimidine is a methyl derivative of sulphadiazine It is also described as Sulphamerazine or Sulphamerizine Its sulphanilamide coefficient is about 20 and its therapeutic activity and toxicity are similar to



sulphadiazine. Solubility 24 mgm per 100 ccm in water at 20°C In the plasma 80 per cent of the drug is combined with protein and only 20 per cent is free For this reason concentration in the tissues is low About 70 per cent of intake appears in urine slowly ... cent in blood have been maintained in monkeys ... d fluid intake is adequate The acetyl deriva ... soluble than sulphadiazine in urine its fæcal ... It is more slowly excreted than the other sulphonamides and an adequate concentration in blood (8 mgm per cent) can be maintained by an initial dose of 4 gm followed by 1 gm every 6 hours It is not effective by the rectal route.

Sulphamera ...
but the inciden ...
sulphadiazine ...
small and infre ...
phylactic purpo ...

(8) *Sulphamezathine* 2 (4 p aminobenzensulphonamido) 4 6-dimethylpyrimidine is a dimethyl derivative of sulphadiazine (Sulphamezathine is a trade name) Its sulphanilamide coefficient is 13



Slightly soluble in water about 1 in 3000 (190 mgm per cent) and 191 207 mgm per cent in urine at body temperature sparingly soluble in cold alcohol and moderately soluble in hot alcohol Melting point 197°C no decomposition during heating at 150-160°C for 30 minutes Its potency is more or less the same as other compounds of sulphadiazine series though it is said to be more potent against pneumococcal infections

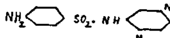
diffuses less readily into tissues than sulphadiazine

Sulphamezathine is the least toxic of the sulphonamides and this fact combined with its comparatively high potency make it a most suitable drug for routine use It is said to be particularly indicated in pneumococcal infections of all grades of severity It does not diffuse readily into the spinal fluid sulphadiazine is therefore to be preferred for meningitic infections The rapid excretion and ready solubility of the drug in the urine (115 to 176 mgm per cent) make it particularly suitable for use in the treatment of infections of the urinary tract Crystals do not form in urine and between 70 and 90 per cent of the drug can be recovered from the urine

Sulphamethazine is the least toxic of the sulphonamide drugs vomiting cyanosis and headache being present in 1 1 per cent of cases and rashes and drug fever only rarely No cases of blood and renal damage have been met with

This drug is most suitable for routine use in all infections particularly pneumococcal in origin on account of its high potency and low toxicity It is not likely to be useful in intestinal infection owing to its rapid and complete absorption nor is it as suitable as sulphadiazine in meningitis because of its low diffusibility into the cerebro spinal fluid

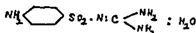
(9) *Sulphapyrazine*, 2 sulphanilamidopyrazine Has a sulphanilamide coefficient of 50



Absorption from the intestine is moderately slow, maximum blood concentrations of 5 mgm per cent being reached in 4 to 6 hours The drug is as active in vitro against *B coli* and pneumococci as sulphathiazole In experimental animal infections it proved as active as sulphathiazole against streptococci and pneumococci and as sulphadiazine against staphylococcal infections It is largely excreted in fæces and concentrations like sulphaguanidine can be obtained with half the dose

Sulphapyrazine has not yet been sufficiently employed in clinical practice for adequate evaluation of its efficacy Reports however, indicate that the drug may prove more effective in the treatment of bowel infections such as dysentery especially in the carrier stage than any of the other sulphonamide compounds

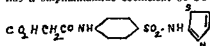
(10) *Sulphaguanidine* (B P , U S P Sulphanilylguanidine) p aminobenzenesulphonylguanidine is also described as Guamide



Solubility in water at 25°C about 1 in 1000, at 100°C about 1 in 10 Sparingly soluble in alcohol and in acetone Insoluble in aqueous solutions of sodium hydroxide Melting point 190-192°C This compound is incompletely absorbed from the gastro intestinal tract, and it is therefore useful for the treatment of bacillary dysentery and similar infections A dose of 6 0 gm followed by 3 0 gm every 4 hours prescribed in adults produces a blood level of 5 0 mgm per 100 ccm less if diarrhœa is present The dose may be reduced to 3 0 gm 8 hourly when diarrhœa has ceased In plasma 8 per cent is combined with proteins and 40 per cent is acetylated Diffusions into the tissues occurs in the same concentrations as in blood It is rapidly excreted in the urine (15 to 53 per cent of intake) but crystals occur in urine frequently A concentration of 1 per cent in the fæces for 6-9 days reduces the number of *B coli* in the stool For this reason it is used to reduce bacterial contents in surgical operation of the gut and in the treatment of bacillary dysentery Concentrations of 400 to 4 000 mgm per cent are found in the fæces after an oral dose of 6 gm Toxic symptoms are slight and infrequent, occasional nausea and vomiting headache, drug fever dermatitis or conjunctivitis may occur Rarely agranulocytosis, hæmaturia and oliguria may occur

(11) *Irgafen* N1 3 4 dimethyl benzoyl sulphanilamide has a sulphanilamide coefficient of 50 It is effective against hæmolytic streptococci pneumococci and staphylococci but has no action against *B coli* It is excreted more slowly than sulphadiazine and thus produces a high blood level This compound has not yet been tried on a large scale

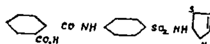
(12) *Succinylsulphathiazole* 2 (p succinyl aminobenzenesulphonamido) thiazole (sulphasuxidine , Colistatin), has a sulphanilamide coefficient of 0 6



It is soluble in alcohol acetone and sodium bicarbonate solution but very insoluble in water It is poorly absorbed in the intestine, only about 5 per cent of the ingested drug being excreted by the kidneys and the concentration in the blood is always low Its action is principally on the coliform organisms in the lumen of the bowel which become greatly diminished in number There is evidence that this effect is due to the liberation of small amounts of sulphathiazole Succinylsulphathiazole has been used mainly for the treatment of dysentery and in the preparation of patients for operations on the large intestine It is less toxic than sulphaguanidine and as effective in the treatment of bacillary

dysentery doses of 6 gm 4 hourly for the first day and 3 gm 4 hourly thereafter produce a concentration of 85 200 mgm of free sulphathiazole per 100 ccm of fæces Fewer toxic reactions than sulphaguanidine are encountered.

(13) *Phthalyl sulphathiazole* 2-(p phthalylaminobenzenesulphonamido) thiazole also known as sulphathalidine closely resembles succinylsulphathiazole It is almost insoluble in water but its sodium salt is soluble



The absorption is even less than that of succinyl sulphathiazole and is said to be non toxic by mouth It is effective against coliform organisms in the dog's intestine and has been found to be effective in the treatment of bacillary dysentery in man.

(14) *Marfanil (Homosulphanilamide)* is 4 aminomethylbenzenosulphonamide or p sulphonamidobenzylamine Marfanil is the German trade name and it is known as sulphabenzamine and sulphamylon. It is freely soluble in water It has been widely used in

Marfa



Germany and elsewhere for local application to wounds Its action differs from other sulphonamides in that it is not abolished by p-aminobenzoic acid or by the presence of pus or necrotic tissue The drug is more effective against anaerobic organisms particularly *Cl welchii* no action on *B coli* It is excreted too rapidly and is thus not suitable for internal use It is used against sulphonamide resistant streptococci

(15) *Sulphanilylbenzamide* (M P 181°C—182°C) was found to be the best bacteriostatic agent next to Sulphat absorbed in blood and quickly excr favourably about its bacteriostatic included strains of Sonne, Flexner strains are found to be most resi strains somewhat resistant While types

4 Pharmacological action of sulphonamides

(1) General action and toxicity

The pharmacological action of sulphanilamide has been described in detail as a typical example of the sulphonamide group of drugs

compound

Sulphanilamide hydrochloride is a relatively inert substance. In small dose it first stimulates and then depresses the central nervous system the depression being manifested by motor paralysis and partial narcosis

Small intravenous doses cause a strong stimulation of the respiratory centre whereas large doses depress it but these effects may have been due to the acidity of the solution of the compound Death is caused either by paralysis of the respiratory centre or by cardiac standstill since the drug depresses the heart muscle directly In cat dilatation of the heart diminution in the amplitude of cardiac contractions arrhythmia and finally cardiac standstill in diastole are produced The isolated rabbit's heart also responds to the drug with a diastolic standstill

Large intravenous doses produce in animals a fall in blood pressure mainly due to depressant effect on the heart and partly also to dilation of the vessels of the splanchnic area Smooth muscle is depressed by the drug while skeletal muscle such as isolated gastrocnemius of frog is contracted in very dilute solution In more concentrated solution the contracture disappeared as well as the ability to react to electrical stimuli

As in the case of other aniline derivatives these drugs produce a fall of body temperature in rats probably due to increased dissipation of heat from the skin There is also a corresponding depression in the gaseous metabolism and a reduction of the respiratory quotient

Briefly small doses of sulphanilamide hydrochloride first stimulate and then depress the central nervous system the depression being manifested by motor paralysis and partial narcosis Relatively small intravenous doses produce stimulation of the respiratory centre, whereas large doses produce depression and finally paralysis The heart is depressed and finally stops in diastole

Toxic effects in animals—Although in man toxic effects are produced even by therapeutic doses of sulphanilamide, its acute toxicity in mammals is low The single oral dose of prontosil tolerated by mice was found to be approximately 0 5 gm per kilo and the subcutaneous dose was one quarter of that amount Mice tolerated 2 0 gm per kilo of prontosil II orally or intravenously and 4 0 gm per kilo subcutaneously The toxicity of sulphanilamide was found to be of the same order, since mice tolerated approximately 2 0 gm per kilo either orally or subcutaneously rabbits 1 0 gm per kilo orally rats 0.2 to 0.4 per kilo intravenously P benzylaminobenzene sulphonamide was less toxic, disulphanilamide certain anilides, sulphones sulphides, disulphide, have all been tested and have more or less the same toxicity

(2) Absorption, distribution, fate and excretion.

ide

Both in animal and human subjects sulphanilamide when given by the mouth is quickly absorbed and the process is complete in 1 to 3 hours. Absorption is quicker if given in solution than in capsules or tablets Alkalies hasten absorption After a single dose the peak in blood concentration is reached in 3 hours thereafter the concentration falls gradually to zero during the following 24 hours With repeated administration at intervals of 4-6 hours a blood concentration of 2 to 10 mgm per 100 ccm can be obtained and maintained The optimum effective blood concentration is 10 mgm per 100 ccm and this is obtained by a dosage scale of 1 gm per day to every 20 lbs of body weight (Long and Bliss), that is about 7 gm for an average individual of 10 stone weight Children require 50 per cent more than this and infants three times as much (Banks) Subcutaneous injections do not give a higher concentration in the blood than obtained by oral administration

taken up from the gut only 5 per cent of the dose is recovered from the urine

circulation sulphanilamide is distributed It penetrates readily into the cerebrospinal ncentrated in any particular organ or tissue double the concentration than that in the

ds

ha

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id

Occurrence in blood tissues, etc

all the fluids and tissues of the salicylates or urea The distributio and fat contain relatively less Th blood The drug seems to be sele the concentration here is 50 per cent to normal body fluids aqueous and exudates In normal secretions of amounts As might be expected

readily into fœtal blood and amniotic fluid It has been found in the human breast milk

... subjects

In the blood ...
acetyl group

refers to unchanged plus conjugated compound

The point of practical importance is that many of the acetyl derivatives are less soluble than original compounds and consequently during excretion through the kidney they tend to crystallise and block the urine passages The extent to which acetylation occurs varies with different compounds and with the time from commencement of treatment Sulphanilamide and sulphapyridine are more readily acetylated than sulphathiazole 20 per cent of the compound in the blood and 25 to 60 per cent of that in urine is in the conjugated form

It has recently been shown that though the alkali reserve falls after administration of sulphanilamide and bicarbonate is excreted in the urine the pH of the blood nevertheless remains constant or even rises

Concentration in bl...
into the ...

Conc blood

to rapid excretion and
of this rapid excretion
every 4 hours in order constantly to maintain an adequate level of concentration in the blood for successful therapy The excretion of the other compounds such as sulphapyridine and sulphathiazole proceeds somewhat more slowly it is slowest in case of sulphadiazine which takes more than three days to eliminate only 30-80 per cent occuring in urine

Briefly sulphanilamide is excreted by the kidneys both in free and conjugated forms chiefly by glomerular filtration The rate of elimination depends on the urine flow and not on the plasma level and hence it is possible to wash out the drug by promoting diuresis Of the drug in the glomerular filtrate 70 to 80 per cent is reabsorbed by the tubules Diuresis will thus favour excretion of the drug and a state of impaired renal function will have the opposite effect After a single dose the excretion is complete after three days After the same period with repeated doses a state of equilibrium is obtained between the amount of drug taken and the amount eliminated To obtain an adequate concentration in the blood it is necessary to use the drug at first in larger doses and then smaller doses repeated at frequent intervals

The
Ther
and
to be ... sulphathiazole is very readily excreted in the urine and it is sometimes difficult to maintain proper concentration in the blood. The diazines are less rapidly excreted Crystalluria is common with sulphathiazole and diazines All compounds readily penetrate the tissue and occur in body fluids and excretions

As in the case of other aniline derivatives these drugs produce a fall of body temperature in rats probably due to increased dissipation of heat from the skin There is also a corresponding depression in the gaseous metabolism and a reduction of the respiratory quotient

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... In conditions ... at slowly less ... o per cent of ... while the rest is excreted in the faeces in high concentration Little or none of succinylsulphathiazol is taken up from the gut only 5 per cent of the dose is recovered from the urine

Distribution—After absorption ...

bound to the plasma ... aly o per cent is said to be thus bound with sulphathiazole about 75 per cent

... penetrates ... l or ... bone ... hole ... for

blood ... absorbed on to the corpuscles ... In addition the concentratio... to normal body exudates In n... amounts As n...

chemotherapeutic property of prontosil could not have been discovered except by trial in infected subjects but in the case of sulphanilamide bacteriostatic action was observed by in vitro tests when using a small number of micro-organisms for the inoculum Thus Colebrook and his colleagues (1936) obtained bacteriostatic action with sulphanilamide in human blood and in human serum In human blood 15000 streptococci added to 1 ccm of blood containing ere destroyed partially in six hours an btained in the blood with its leucocytes ater than the bactericidal effect of norm the bacterios tatic power of the blood feeding with sulphanilamide For example after the oral administration of 4 gm of sulphanilamide to a monkey the blood was shown 3½ hours after its administration to be 1000 times as bacteriostatic as normal monkey blood after 24 hours it was only 100 times and after 48 hours the power was only slightly above that of the normal animal Similar results were obtained in man by the same observers The blood of one normal person collected 2 hours after being given 1 5 gm of sulphanilamide orally was shown to cause complete destruction of 7200 streptococci in 100 ccm of blood whereas before treatment the same person s blood could not prevent 28 streptococci from multiplying to a very large number in 24 hours

Prevention of multiplication of organisms The sulphonamides act upon susceptible micro-organisms by their bacteriostatic rather than bactericidal action that is to say their multiplication is prevented If the multiplication of micro organisms can be held in check for sometime the defence mechanisms of the body can usually overcome the infection by destroying the invading bacteria The clinical response to sulphonamides is rapid when the defence mechanisms are efficient and the infecting bacteria are sensitive to the drugs Direct bactericidal action is probably not produced by concentration of sulphanilamide reached in the tissues with doses given clinically but recovery may occur without complete eradication of the infecting organism from an original focus and this probably accounts for relapses

It should be clearly understood that sulphonamides do not neutralise bacterial toxins to any great extent though there is some evidence that they may inactivate certain endotoxins

Leucocytes have been shown to be essential for bactericidal action of these drugs It has been shown that the presence of leucocytes in the culture medium allows otherwise bacteriostatic concentrations of the drug to kill the organisms In vivo it has been shown that active phagocytosis occurs in recovery from infection with sulphanilamide therapy In mice with granulopoenia even intensive sulphanilamide therapy does not cure infection with haemolytic strep therefore an essential part of the sterilis in infections in animals The action of the bacteria which are altered in such a ocytosis The drug does not in any way rophages

Sulphanilamide does not enhance the bactericidal value of human serum nor does it promote antibody formation It does not probably hinder it either The treated animals show no immunity upon re-infection

Changes in bacteria—Morphological changes are produced in micro-organisms when acted upon by sulphanilamide, streptococci may show increased length of chains swelling and alteration of staining reactions Meningococci swell up become irregular and pyriform in shape and show staining abnormalities The changes however, do not appear to alter their virulence when injected into animals. Such morphological changes suggest that sulphanilamide depresses the

(3) Action on micro-organism

(a) *In vitro action against bacteria*—Prontosil was found by Domagk to be ineffective against bacteria *in vitro* even in high concentrations, but was active *in vivo* against the same organisms Later work showed that in concentration of 1 in 10 000 sulphanilamide has bacteriostatic action against hæmolytic streptococci, pneumococci *Cl welchii* and *Brucella melitensis* In concentrations higher than 1 in 1 000 it has a bactericidal action also against some other organisms When the culture media employed are less favourable for growth higher concentrations of sulphanilamide have a bacteriostatic or even a bactericidal effect on staphylococci and a number of gram negative organisms It is for this reason that sulphanilamide is useful in urinary infections

Sulphapyridine inhibits the growth in vitro of large inocula of pneumococci in leucocyte-free human blood in concentration of 1 in 250 000 to 1 in 8 000 When leucocytes were present concentrations of 1 in 32 000 killed the organism It is therefore more effective than sulphanilamide It is also more effective against hæmolytic streptococci *E coli* and *E typhi*

Sulphathiazole has marked bacteriostatic action against streptococci as well as staphylococci It also acts on *Str faecalis* which is not acted on either by sulphanilamide or sulphapyridine Sulphathiazole and thiazole derivatives have the most powerful bacteriostatic action of all sulphonamide drugs on colon typhoid dysentery group Growth of both hæmolytic and non hæmolytic enterococci is inhibited

(b) *In vivo action*—A large volume of work was carried out with sulphanilamide and other compounds on experimental animals It was shown that sulphanilamide was effective against group A of hæmolytic streptococci which cause a large number of human infections Infections in mice with Group B are resistant Group C are moderately susceptible Infections with

perimental poliomyelitis in monkeys dog distemper were not ... pathia venerium infections in mice and guinea pigs were beneficially affected

Sulphapyridine was more effective in vivo in pneumococcal, staphylococcal and meningococcal infections in mice than sulphanilamide Sulphathiazole is quite effective against pneumococcal staphylococcal streptococcal and meningococcal infections

5. Mode of Action of Sulphonamides

(1) *Direct or indirect action*—When dealing with the mechanism of the action of any chemotherapeutic agent it is of prime importance to learn on the one hand, as to what ... tent ... ince ... e in ... sms ... it ... ody

or that unknown in vivo factors have enhanced its action This is exactly what was ...ound in the experiments with prontosil In the test tube prontosil was practically inert but in experimental tests in mice it was found to exercise a powerful action which quickly freed the tissues of *Str haemolyticus* and effected a cure Prontosil is believed to be reduced in the body to sulphanilamide which is said to be the effective agent. The

chemotherapeutic property of prontosil could not have been discovered except by infected subjects but in the case of sulphanilamide, bacteriostatic action was obse in vitro tests when using a small number of micro organisms for the inoculum Colebrook and his colleagues (1936) obtained bacteriostatic action with sulpha in human blood and in human serum In human blood 15 000 streptococci a in a concentration of 1 in 12 000 were d 24 hours Similar effects were obtained bacteriostatic effect was much greater t d The same observers stated that the b and monkeys could be increased by feed oral administration of 4 gm of sulphanila a monkey the blood was shown 3½ hours after its administration to be 1,000 t bacteriostatic as normal monkey blood after 24 hours it was only 100 times ar 48 hours the power was only slightly above that of the normal animal Similar were obtained in man by the same observers The blood of one normal person 2 hours after being given 1 5 gm of sulphanilamide orally was shown to cause destruction of 7 200 streptococci in 100 ccm of blood whereas before treatment t person s blood could not prevent 28 streptococci from multiplying to a very large in 24 hours

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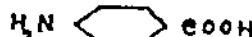
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metabolic activity in the body of the bacteria which is essential for invasion of animal tissues It is suggested that sulphanilamide is converted into a substance which combines with the proteins available for bacterial nutrition rendering it unfit for assimilation

(2) *Role of para-aminobenzoic acid*—The action of sulpnonamides can be neutralised by small concentrations of p-aminobenzoic acid



or less effectively by certain other compounds such as methionine or even peptones It would appear that p aminobenzoic acid is essential for the growth of bacteria and while most of the bacteria can synthesize this compound for some others it must be supplied from outside and is therefore a growth factor The sulphonamides are sufficiently similar in chemical composition to p amino benzoic acid to be used instead by the bacterial organisms if present in greater concentration They do not, however, serve the metabolic functions equally well and the result is interference with bacterial multiplication

The enzyme-system has a greater affinity for p aminobenzoic acid than for sulphonamides and therefore to be effective the sulphonamides must be present in much greater concentration It has been calculated that to counteract in vitro one part of p aminobenzoic acid, a concentration of 1 600 parts of sulphanilamide, 100 parts of sulphapyridine 36 parts of sulphaguanidine is required Pus and necrotic tissue contain substances antagonistic to the ' therefore these drugs exert less effect o wounds containing pus or sloughs iave also been demonstrated in fresh muscle, spleen and pancreas and in pleural pericardial and synovial fluids, such substances may interfere with the therapeutic action of the drugs in vivo

The action of sulphonamides can also be neutralised besides p aminobenzoic acid by *other chemical compounds containing the p-aminobenzoic acid group although less rapidly* Examples of these compounds are procaine (the d ethylamino ethyl ester of p aminobenzoic acid also known as novocain, planocaine etc) larocaine tutocain butyn benzocaine (anaesthesin) and orthocaine (orthoform) If these particular local anæsthetic drugs are used at the same time as sulphonamide drugs the effect will be weakened It should be borne in mind that these anaesthetics also give the same colour reaction as the sulphonamides in Bratton and Marshall s test they should not therefore be employed in obtaining samples of cerebrospinal or other fluids for estimations of the drugs

Such local anaesthetics which do not contain p aminobenzoic acid group *e g* cocaine tropacocaine benzemine (eucaine) amylocaine (stovaine) nupercaine phenacaine amethocaine (decicaine) and metycaine can be used

Chemical structure and bacteriostatic activity It has been found that shifting of amino group of the sulphonamide compounds from the para to the ortho or meta position removes the bacteriostatic activity of these compounds Substitution of the p amino radical with other groups produces compounds which have no bacteriostatic effects or which are ... example is the case with marfanil the p amino radical abolishes in the liver in producing the separated off in the body as iazole the bacteriostatic activity amido group may increase the ctivity varies with the type of if this group is acyclic as in group is used and maximum phapyridine, sulphadiazine and tero atoms as in sulphathiazole

(3) *Ionic dissociation*.—The sulphonamides undergo ionic dissociation in solution and behave to a certain extent like weak acids their activity probably depending not upon the whole molecule but only upon the anion Within certain limits the bacteriostatic activity tends to be greater in alkaline solutions since more ions are available under these conditions Sulphonamides which are about 50 per cent dissociated at the reaction of the body fluids *e g* sulphathiazole tend to be more active than those in which dissociation is about 3 000 times less *e g* sulphanilamide Although for this and other reasons the action of some sulphonamides is quantitatively greater than that of others there is little evidence for a qualitative difference apart from the exceptional case of Marfanil whose mode of action is different The fact that sulphanilamide is effective against streptococci sulphapyridine against streptococci and pneumococci and sulphathiazole and sulphadiazine against streptococci pneumococci and staphylococci is according to many authorities due not to the action of any particular drug being specific for certain organisms but rather to the less susceptible organisms such as pneumococci and staphylococci responding only to the more active compounds The differing rates of absorption and excretion do render the use of certain compounds advantageous for certain types of conditions thus sulphanilamide on account of its ready solubility is useful for local application to wounds though the less soluble sulphathiazole has greater bacteriostatic power Sulphadiazine produces particularly high blood concentrations because of its slow excretion while sulphaguanidine and phthalylsulphathiazole are effective against organisms in the lumen of the lower part of the alimentary canal because they are either very slowly or incompletely absorbed and for that reason reach this region in high concentrations The differences in the fields of usefulness of the various compounds probably depend much more upon differences in their physical and pharmacological properties than upon any specificity between drugs and bacteria

(4) *Drug resistance*.—When micro organisms are exposed in vivo or in vitro to concentrations of sulphonamides which are not potent enough to destroy them all the survivors *often become resistant to the further action of these drugs* The organism may eventually become capable of growing in comparatively high concentrations of the drugs under suitable conditions This acquired resistance of bacteria to sulphonamides is analogous to the well known arsenic resistance which may develop in trypanosomes and also like trypanosomes once it is established it persists through many generations of the bacteria This phenomenon has been shown to occur in case of pneumococci gonococci streptococci B coli and dysentery bacilli and probably also in other bacteria but its frequency in clinical practice has not been established Cases have been described of pneumococcal infections which underwent prolonged treatment with sulphonamides and which eventually became completely resistant but when short intensive courses are given the development of drug resistance is probably rare In any case care should be taken to avoid fostering the development of drug resistance in the infected by avoiding prolonged treatment with small doses of sulphonamides Once organisms have become resistant to any sulphonamide compound they become correspondingly resistant to all the other sulphonamide compounds (except Marfanil) but it may be found that a more active sulphonamide *e g* sulphathiazole will still exert some antibacterial action when less active compounds *e g* sulphanilamide have proved ineffective Bacteria which have become resistant to sulphonamides still retain their original sensitivity to compounds of other types *e g* penicillin gramicidin the acridine antiseptics etc

(5) *Estimation of potency of sulphonamides*—Estimations of potency in vitro are determined by measuring the minimal concentration required to inhibit the growth of a susceptible organism Using a standard inoculum of *B coli* it was found that while the necessary concentration varied when different media were employed the relative proportion for different drugs was always the same These proportions were also found to correspond to the *in vivo* activity based on figures obtained from effective blood concentrations and percentage survivals It has also been shown that the bacteriostatic potency of a sulphonamide compound is in proportion to its ability to counteract the antibacteriostatic action of p-aminobenzoic acid Wood (1942) found that the relation of the minimum amount of p aminobenzoic acid required to prevent bacteriostasis to the concentration of sulphonamide used was constant despite wide variations in the latter He used the term *bacteriostatic constant* which equals molar concentration of p aminobenzoic acid/molar concentration of sulphonamide at which bacteriostasis is just prevented He employed an inoculum of 10 000 viable *B coli* in plain synthetic broth at 37°C and took readings at the end of 5 days An alternative and more satisfactory method of expressing the potency is the *sulphanilamide coefficient* the bacteriostatic constant of sulphanilamide/the bacteriostatic constant of the sulphonamide compound under test or the minimum bacteriostatic concentration of sulphanilamide/the minimum bacteriostatic concentration of the sulphonamide under test

The average Sulphanilamide Coefficient adjusted to constant range taking figures from a number of workers who used *B coli Staph aureus* pneumococcus type I and III is given below —

Sulphanilamide	1
Succinyl sulphathiazole	0.6
Sulphaguanidine	4
Sulphacetamide	8
Sulphapyridine	13
Sulphamezathine	13
Sulphamerazine	20
Sulphadiazine	36
Sulphapyrazine	50
Sulphathiazole	50

The consensus of opinion at present is that sulphadiazine and its homologues sulphamethazine (sulphamezathine) and sulphamerazine are the most effective and the least toxic of these compounds On account of their comparatively slow excretion the interval between doses can be increased to 6 to 8 hours which is

6 Routes of administration

(1) Oral route

The sulphonamide drugs are usually given by the oral route In order to facilitate absorption the tablets must be crushed and taken with half ... ate and sodium citrate 30 g ... the mouth should be thorc ... der from the crevices

of the mouth If the patient is in a state of coma the drugs are given by nasal catheter or by the stomach tube the powder being sufficiently diluted to prevent the sediment from blocking the tube

The oral route is the method of choice because of its simplicity and practicability and it should always be used unless it is contra indicated by the condition of the patient It has been shown that approximately the same concentration of sulphanilamide was obtained in 3 to 5 hours after administration of the same amount of drug by either the oral or the subcutaneous route

Rectal or subcutaneous administration is used as a substitute for oral administration when this method cannot be used as for instance after operation in the region of the stomach when there is no need to raise the blood concentration readily

(2) Parenteral route

(a) *Subcutaneous administration*—The subcutaneous route is useful in cases of persistent nausea and vomiting where hypodermoclysis is indicated It is also useful in rapidly building up the desired concentration of the drug in the blood when the oral route has failed to do so

(b) *Intramuscular administration* is used as a substitute for intravenous administration when good veins are not available or for some other reasons intravenous injection is not desirable This method is less satisfactory and certain amount of risk is involved with the sodium salts of sulphapyridine sulphathiazole and sulphadiazine on account of the high alkalinity of the solution It has no particular advantage over the subcutaneous route

(c) *Intravenous administration*—This route has no justification in routine treatment [illegible]

(3) Strength of solutions

Solutions of sodium salts of the sulphonamides may be used for intravenous or intramuscular injections except in the case of sulphanilamide where no such salt is available The sodium salts of sulphathiazole or sulphapyridine are given in 10 per cent solution and for sodium sulphadiazine 5 per cent solutions are recommended As these solutions are highly alkaline they are liable to set up irritation and necrosis when they escape into the tissues They can however be given intravenously and if they are given very slowly and no material is allowed to escape outside the vein no deleterious effects are produced Intramuscular injections are liable to produce considerable damage and if it is necessary to use this route the number of injections should be as few as possible and the distance between the site of each injection should not be less than three inches. The injections should be given deep into the muscles and as far away as possible from the important nerves, vastus externus muscle is usually selected for this purpose as it has no important structure underneath If injections are given in the neighbourhood of a large nerve such as the sciatic, serious damage may occur Solutions of sodium salts should under no circumstances be given intrathecally

Sodium salts of sulphapyridine and sulphathiazole are supplied in powder form in ampoules containing 1 0 gm each Both for intravenous and intra muscular injection the contents of an ampoule are dissolved in 10 ccm of sterile distilled water immediately before use Sodium sulphadiazine is usually supplied in bottles containing 5 0 gm each and a 5 per cent solution can be freshly prepared It is rarely necessary to give more than one intravenous injection but in cases of persistent coma or vomiting injections must be continued 3 5 gm are given every 12 hours for an average adult of 60 kgm (9½ stone) weight Sodium salts have also been given by continuous drip infusion in saline

A saturated solution of sulphanilamide (0 8 per cent) is prepared by dissol ving 1 0 gm of the crystalline sulphanilamide in 125 ccm of sterile physiological saline solution This solution can be given by the intravenous route or by continuous drip method The soluble form of sulphanilamide known as sulphanilamide L S F which is issued in 15 per cent solution in ampoules may be used for parenteral injections

By adding excess of sulphanilamide to warm water (26 gm to a Winchester bottle of 2 250 ccm capacity) and allowing it to cool at room temperature a saturated solution is prepared The supernatant fluid is decanted off and will contain about 0 8 per cent of sulphanilamide The solution containing the required quantity of this drug is diluted to 300 ccm (10 fl oz) with one per cent glucose in physiologic saline or physiologic saline alone Per rectum the drug is given every four hours in slightly larger doses than used for oral administration The concentrations of the drug obtained in the blood by this method are lower than those following oral administration and there is longer time lag Sulpha pyridine should not be given by the rectal route Sodium salts of sulphapyridine *sulphadiazine or sulphathiazole are given by the subcutaneous route when* administration by the mouth is not possible 5 0 gm of the salts being given by continuous c
are 10 and 9
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variations

7. Dosage of sulphonamide drugs

General scheme of dosage—The effective dosage in the case of important sulphonamide drugs in use has been given under individual drugs at the beginning of this section Medical Research Council War Memorandum No 10 (1945) has laid down a scheme of dosage for curative and prophylactic purposes as result of experience gained both in Civil and Military practice This authoritative scheme is reproduced below —

The dosage given is suitable for subjects of average weight who are given sulphanilamide sulphathiazole sulphadiazine sulphadimethyl pyrimidine or sulphapyridine if tolerated somewhat smaller doses are required in case of sulphamerazine The weight of the average adult may be taken as 60 kgm (9½ stone) if there is wide departure from this corresponding allowances in dosage should be made Children weight for weight have a better tolerance than adults for sulphonamide drugs In infants tolerance per unit of weight has been estimated as
table is intended for g
often have to be modi
of the drug given the manufacturers own recommendations regarding dosage will be of help here and should be carefully considered especially in case of the newer sulphonamides'

DOSAGE OF SULPHONAMIDES

Severe Infection (endangering life)

	Adults	Children 0-3	Children 4 10	Children 11 15
Initial dose	2 4 gm intravenously 1 5 gm by mouth	0 5 gm intravenously 0 5 gm by mouth	1 gm intravenously 0 75 gm by mouth	1 2 gm intravenously 1 gm by mouth
Followed by — 1st period 2 3 days	1 5 gm 4 hourly	0 5 gm 4 hourly	0 75 gm 6-hourly	1 gm 4 hourly
2nd period 2 days (approximately two third of dose of 1st period)	1 gm 4 hourly	0 5 gm 6 hourly	0 75 gm 6-hourly	1 gm 6 hourly
3rd period 2 days (approximately one-third of dose of 1st period)	1 gm 6 hourly	0 25 gm 6-hourly	0 5 gm 6-hourly	0 5 gm 6 hourly

Milder or "Moderate" Infections

	Adults	Children 0-3	Children 4 10	Children 11 15
Initial dose	2 gm	0 5 gm	0 75 gm	1 gm
Followed by — 1st period 2 days (unless otherwise stated)	1 gm 4 hourly	0.5 gm 4 hourly for 12 24 hours	0 5 gm 4 hourly	0 75 gm 4 hourly
2nd period, 2 days (unless otherwise stated)	1 gm 6-hourly	0 5 gm 4 hourly for 3 4 days	0 5 gm 6-hourly	0 75 gm 6 hourly
3rd period, 2 days	1 gm 8 hourly	0 25 gm 6-hourly	0 25 gm 6-hourly	0 5 gm 6 hourly

The duration of a course is normally 6-7 days and it should rarely be prolonged beyond the seventh day

Prophylactic dosage

"This will vary according to circumstances but some examples may be given —

"(a) For children undergoing tonsillectomy when the presence of a streptococcal infection is suspected or known —

Drug Sulphanilamide	Ages 4-6	Age 7 15
Pre operative dose, given 2 hours before the operation — — —	1 gm	2 gm
Post-operative doses starting 4 hours after the operation and continuing at four hourly intervals for 2 days — — — —	0 25 gm	0 5 gm

"(b) For women in labour when there is known risk of infection by hæmolytic streptococci —

Drug Sulphanilamide

First dose at beginning of labour — —		2 gm
First day at 4 hourly intervals beginning 4 hours after the first dose — — —		0 5 gm
Second and third days at 6-hourly intervals —		0 5 gm

(c) *To prevent urinary tract infection* e g when an indwelling catheter is requ red for some days —

Dose 1st day — — — —	1 gm 4 hourly	0 5 gm 4 hourly
Subsequent days — — — —	1 gm 6-hourly	0 5 gm 6-hourly

Summary of dosage —

In severe illness For first 2 or 3 days 9 gm daily second 2 or 3 days 6 gm da ly and third 2 or 3 days 3 gm daily Total 40 to 50 gm

In mild illness For first 2 or 3 days 6 gm daily second 2 or 3 days 4 gm da ly and third 2 or 3 days 2 gm daily Total 24 to 32 gm

For children of six years half the adult dose for a child of three years and under one th rd of the adult dose

An initial loading dose (4 3 gm in adults) should always be given when treatment is begun

(d) There is no evidence that the sulphonamides are effective aga nst the primary infection in influenza measles and pertuss s The drugs may however be used to control the secondary complicat ons—in particular acute otitis med a, bronch tis and broncho pneumonia—which commonly follow As the complicating infections may be due to one or other of a variety of pathogens—hæmolytic strept
influenza bacillus—one of the more generally active
Experience favours the giving of the drug at the
than as a routine prophylactic in every case There
incidence of bronchopneumon a and suppurative oti
reduced by routine prophylaxis with sulphathiazole
from the appearance of the rash (Banks Practit
prevent infections from being occasionally contracted from other patients after the drug is stopped

Dose	0-2 years	2-6 years
—	0 25 gm	0 5 gm
	6 hourly	6-hourly

In severe infections best results will be obtained if the concentration of the drug in patients blood attains a certain level This should therefore be deter mined during the first two or three days *6 to 12 hours after beginning of treatment*
... It s not al ays possible to insure the desired
...re great variations in the

Vomiting if it occurs is also another fac
are given The estimation of sulphonan
micromethods have been introduced to make it possible to obtain a rough estimate of their concentration even from a drop of blood from the finger or the lobe of the ear The importance of these estimations during early stage of exhibition of these drugs is that they will give a warning if the dosage is inadequate without waiting for clinical indications *which may be difficult to interpret If a patient* does not respond to treatment for three or four days the estimation of concen
tration o ... the sensitivity of the organism
may exp ... further action While estima
tions of ... it in severe infections *it is not*
essential ... s or that the drug should be
withheld if laboratory facilities for such examinations are not available

8 General considerations regarding use of sulphonamides.

The first important point is that in the treatment of acute infections a large initial or loading dose of drug should be given in order to get the blood concentration of the compound to an effective level as carefully as possible In very severe cases it is desirable to do this by giving the first dose either intravenously or intramuscularly

The reasons for this are —

(1) The sulphonamides are much more effective on a smaller number than on a large number of micro-organisms It is well known that hæmolytic streptococci are able to multiply in human tissue fluids If however an effective dose of sulphonamide is given during the rapid growth phase acute infections are likely to be aborted before any serious damage is done and before the establishment of the suppurative stage which is much less amenable to treatment with sulphonamides

(2) It has been shown that sulphonamides have a more marked antibacterial action at fever temperature than at the normal temperature of the body

(3) It is also possible that exposure of micro-organisms to gradually increasing dose of sulphonamides as would occur if the patient is treated with small doses may produce development of drug resisting strains The possibility of this contingency is much less if the drugs are given in full therapeutic doses from the very beginning

It should be clearly understood that the greater the risk to life from the infection the larger the dosage required Doubling the dose however does not double its therapeutic effect, but probably increases it only by a 5th to 3rd Further higher doses require greater precaution against the deleterious effects of the drug and frequent leucocyte counts to give warning of agranulocytosis have to be done Sufficiently larger quantities of fluid to insure larger quantities of urinary secretion so as to minimise the risk of blockage of urinary passages must be taken The fluid intake should not be less than five pints (3 000 ccm) daily in an adult and to this the amounts lost through vomiting diarrhoea or sweat should be added It should be appreciated that in India during the hot weather 3 pints or more may be lost by profuse sweating The criterion to be kept in mind is that under no circumstance should the output of urine be allowed to fall below 50 ounces (1500 ccm) per day

Medical Research Council War Memorandum No 10 lays down the following detailed directions regarding the amount of fluid to be taken —

" With all the usual sulphonamides except sulphanilamide sulphacetamide and probably [illegible] (1 pint) 3 5 liters of over [illegible] ant thing [illegible] nieved by [illegible] f sodium [illegible] of alkali should be given."

"The maintenance of a large fluid intake during sulphonamide therapy has the added advantage of assisting solution of the drugs in the upper part of the alimentary tract"

Combined Therapy —It has been pointed out that it is advantageous to administer two or more compounds conjointly in the treatment of severe infections This permits usually smaller doses of each compound than ordinarily required of either drug alone with

possible prevention or reduction of toxic reactions It is also said that this reduces chances of production of drug resistance in the organism concerned in infection Experiments on mice show that the compounds probably act *synergistically and additively* A *mixture of* equal parts of sulphathiazole sulphadiazine and sulphameraz ne is said to reduce or elim nate renal obstruction due to crystalluria without administrat on of alkalis Allergic reactions (drug rashes fever etc) are also less and blood and urine concentrations are higher

A combination of sulphadiazine and sulphamerazine has been recommended the in tial dose being 0 09 gm per kilo body weight for patients we ghing upto 40 kilo Beyond that the initial dose is 4 gm and maintenance dose 1 0 gm every 8 hours day and night

Sulphonamides such as *sulphadiazine* combined with ant biotics such as penicill n or streptomycin are more effective than either drug s ngly

(1) Concentration in blood.

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whether the patient is asleep or awal e Approximate indications of the con centration of various sulphonamides in the blood which are likely to be attained with the dosage recommended are given in the following table —

	Severe infections endangering life	Milder cases	Prophylaxis
	100 ccm mgm per	mgm per 100 ccm	mgm per 100 ccm
Sulphanilamide	7 10	4 6	2 3
Sulphapyridine	7 10	4-6	1 2
Sulphathiazole	6 7	3 5	1 2
Sulphadiazine	10-15	6 10	2-4

These concentrations are likely to be effective in the majority of infections with the sensitive organisms *e g* pneumococcus meningococcus haemolytic streptococcus etc In cases of less sensitive organisms the concentration of sulphonamides in the patient s blood should be higher It should also be remembered that besides a *few micro-organisms developing resistance to* sulphonamides there may be naturally insensitive strains among sensitive organisms The degree of sensensitiveness of the organisms can be determined in vitro and this test should be performed in cases where there is unsatisfactory response to the drug Higher concentrations of sulphonamides in the blood will be required in the treatment of a heavy infection than with an incipient one *As the general condition of the patient improves in acute infections* the dose of the drug should be gradually reduced but it should not go below sub-effective blood level The administration of drug should not be stopped too soon as there is risk of recurrence, at the same time if the drug is not given for two to three days after the temperature comes down to normal it gives a clin cal evidence of recovery The total duration of the course is from 6 to 7 days and *it should be* It is advisable to do a leucocyte count if the 6 days or more than 300 gm of the drug sulphathiazole excluded)

If there is no definite improvement within 3 or 4 days inspite of adequate dosage the concentration of the drug in the blood should be tested and the situa tion with regard to the sensitiveness of the infecting orgnisms to the drug should be determined If the organism is relatively insensitive a more active sulphonamide drug may be given The action of sulphonamides is also inhibited by peptones produced in an undrained pocket of pus or in necrotic tissue in a wound produced by disintegration of cells and bacteria This condition should

be dealt with by drainage The natural defences of the individual may be poor and may not be able to deal with the organism inspite bacteriostasis produced by the drug as occurs in old and infirm people

In sub acute and chronic infection it is not necessary to give a large first dose of the drugs Where prophylactic action is desired smaller doses may be used because there will be fewer microbes to be dealt with in the initial phase of an infection

In urinary infections smaller doses are desirable than in case of general infections because concentration of these drugs in the urine is much higher than in the blood and tissues Total dosage of sulphonamides midnight to midnight is recorded on the patient s temperature chart each day to insure that the drugs are not continued for too long The dose should be recorded in terms of grams and not in terms of tablets

(2) Cautions and contra indications

It was experimentally demonstrated that incidence of sulph hæmoglobinaemia was increased if sulphates and particularly magnesium sulphate was used as a purgative The reason given was that its cathartic effect brought the unabsorbed food into the large intestine where it fermented and liberated sulphides Sulphæmoglobin however is not the common cause of cyanosis and these agents do not increase its incidence Nil lacl (1941) showed that diets including eggs and onions and administration of various sulphates did not appear to have increased the frequency of cyanosis

Pregnancy if present is not a contra indication to the use of sulphonamide drugs although they pass through the placenta and attain the same concentration in the foetal blood as in the maternal blood Prolonged use of these drugs however is not recommended

Sulphonamide drugs are contra indicated where severe toxic reactions have followed their previous use They should be given with caution in cirrhosis of the liver as they give rise to toxic effects more frequently In infectious hepatitis due to susceptible bacteria they are beneficial If anæmia granulopœnia or jaundice are not due to sulphonamides the drugs are not contra indicated

9 Toxic effects of sulphonamides

(1) Introductory

Sulphonamides are very potent drugs and are liable to produce toxic reactions It is necessary therefore to take every precaution when these drugs are being administered

Many of the toxic effects described below do not commonly occur With the exception of crystalluria these are either due to hypersensitivity to the drugs or to their toxicity Serious effects have been produced in the hypersensitive even by transfusion of blood from a donor receiving prophylactic doses of sulphonamides Side effects may not appear for 10 to 14 days Reactions occur earlier in those who have received previous doses of the drug

Skin tests for general sensitivity and patch test for skin sensitivity have been devised

Previous use of drugs—Before beginning treatment with sulphonamide drugs it should be ascertained wherever possible whether the patient had these drugs on any previous occasion and if so whether he suffered from any toxic effects If a drug of this group has been previously taken the amount consumed by the

possible prevention or reduction of toxic reactions It is also said that this reduces chances of production of drug resistance in the organism concerned in infection Experiments on mice show that the compounds probably act synergistically and additively A mixture of equal parts of sulphathiazole sulphadiazine and sulphamerazine is said to reduce or eliminate renal obstruction due to crystalluria *without administration of alkalis* Allergic reactions (drug rashes fever etc) are also less and blood and urine concentrations are higher

A combination of sulphadiazine and sulphamerazine has been recommended the initial dose being 0 09 gm per kilo body weight for patients weighing upto 40 kilo Beyond that the initial dose is 4 gm and maintenance dose 1 0 gm every 8 hours day and night

Sulphonamides such as sulphadiazine combined with antibiotics such as penicillin or streptomycin are more effective than either drug singly

(1) Concentration in blood

The concentration of the drugs in the blood must be maintained at an effective level throughout the 24 hours of the day particularly during the acute phase of infection This means that the drug should be given at 4-hourly intervals whether the patient is asleep or awake Approximate indications of the con*centration of various sulphonamides in the blood* which are likely to be attained with the dosage recommended are given in the following table —

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patient should be taken into account in planning future dosage Patients who have had toxic reactions previously may even get more severe reactions if the drugs are taken again Patients who are hyper sensitive to one sulphonamide compound may not necessarily be *hyper sensitive to another such compound* In such individuals where clinical condition permits delay a small test dose of the drug (0 1 to 0 3 gm) should be given 12 hours before the main treatment is started The patient is carefully watched and if toxic effects appear the drug should be immediately discontinued Cases have been recorded in which first course of sulphonamide treatment produced no ill effects but a second course given weeks or months later produced rigors rise in temperature and prostration This is probably due to the patient becoming sensitized to the drug and this is more common with sulphathiazole than with other drugs Such a possibility should always be kept in mind although hyper sensitivity is not a very common occurrence Hypersensitive patients can be desensitized by giving small initial doses of the drug for 24 hours General hypersensitivity to sulphathiazole has followed after local application of this drug to skin lesions

Toxic symptoms and signs—Patients who are under sulphonamide treatment should be seen by the medical man in charge of the case at least once a day and the early symptoms of toxic reactions, *e g*, headache nausea, vomiting or malaise should be carefully looked for

Cyanosis frequently occurs but it is usually of little serious significance The presence of any rash jaundiced sclerae paleness of mucous membranes (due to acute hæmolytic anæmia) may be observed The temperature of the patients should be carefully recorded Such symptoms as rise of temperature lassitude headache and sore throat especially if they occur after the 8th day suggest acute agranulocytosis, in such cases the drug should be stopped immediately and differential leucocyte counts should be done If after a period of normal temperature fever recurs in the course of sulphonamide therapy the drug should be stopped *or if recently discontinued should not be resumed* unless it is made certain that the fever is due to recurrence of the infection under treatment The blood should be examined for possible granulocytopœnia In cases in which sulphonamide therapy has to be stopped because of toxic reactions large quantities of fluids (5 000 ccm or 9 pints daily) should be given to accelerate excretion of the drug It is advisable not to give fluid by the intravenous route as it is liable to produce œdema of the lungs

Pain in the kidney region and hæmaturia with decreased urine secretions are indications for immediate stoppage of the drugs The risk of kidney affection is particularly great when sodium salts of these drugs are given intravenously and the blood thus becomes flooded with excess of these compounds It is advisable to measure the amount of urine secreted daily when sulphonamides are being administered The reaction of urine and the presence of red blood cells should be regularly recorded *Sufficient quantities of fluids should be given* to obtain a secretion of 1500 ccm (52 oz) of urine in adults output below 1 000 ccm per day should be taken as a danger signal Besides this sufficiently large quantities of sodium bicarbonate citrate or lactate should be given by the mouth to keep the reaction of the urine alkaline The reason for this is that the acetyl derivatives into which these drugs are partly converted in the blood are more soluble in alkaline than in acid urine If hæmaturia is only microscopic it is not necessary to stop the drugs but calls for careful observation T [illegible] the urine [illegible]

renal damage or obstruction Differential leucocyte count should be [illegible]

possible on the 3rd and 5th days after beginning of massive sulphonam[...] therapy intensive treatment with these drugs as a rule should not be continu[...] beyond the 7th day If the severe infection from which the patient is suffer[...] produces leucopoenia sulphonamide treatment should not be withheld but careful watch should be kept by doing frequent blood counts because of the ris[...] of agranulocytosis which is one of the most dangerous sequels of sulphonamid[...] therapy This condition rarely makes appearance before the 14th day of th[...] therapy The total and differential white blood counts should be done at leas[...] twice a week after the 7th day If the polymorphonuclear leukocytes fall below [...] per cent or if the total white cell counts rapidly falls below 4 000 per cmm the treatment should be immediately stopped

(2) Toxic reactions and side effects

Toxic reactions with this group of drugs whether mild or severe commonly occur and a close watch should be kept for them The pathogenesis of these reactions is not clearly understood some being due to the toxic action of the drugs while others are due to hyper sensitivity There may or may not be history of previous use of the drugs Sensitiveness to these drugs occurs from previous use even many years previously Sometime patients sensitive to one drug of sulphonamide group are not sensitive to another sulphonamide As a rule toxic reactions appear after the drug has been used for several days but sometime a violent reaction may be produced immediately after the first dose

Disastrous consequences from the use of these drugs if given judiciously are fortunately not common There is no doubt however that increased number of people are acquiring hyper sensitivity to sulphonamide drugs Toxic reactions are more common with sulphanilamide sulphapyridine and sulphathiazole and less with sulphadiazine The pathological changes produced by sulphonamide drugs have been mostly worked out in animals In a series of eight human fatal cases besides changes in the kidneys the chief lesions were multiple areas of focal necrosis in the liver lungs bone marrow spleen adrenals myocardium and lymphatic glands Insterstitial myocarditis has been recorded from prolonged use

Toxic effects whether mild or severe often occur with heavy doses and in some individuals even with small doses probably due to unsuspected idiosyncracy to the drugs This is specially the case with disturbances of hæmopoietic system e g agranulocytosis whose onset may be very insidious and unless fre[...] ent blood examinations are made the bone marrow may be seriously damaged [...]fore it is recognized Such effects are however not common and often [...]appear when the drug is stopped If however there is severe disturbance [...]he blood blood transfusion may have to be immediately given

The toxic effects produced by different sulphonamides are summarized in following table modified from Medical Research Council Memorandum 10 —

(3) The more important toxic effects in detail

[...]a) *General* —The patient may complain of malaise and discomfort or a [...] which he cannot exactly describe There may be a combination of nausea [...]he tinnitus giddiness lassitude and intense mental depression Such [...]ms are more frequent with sulphanilamide and sulphapyridine and less [...]lphadiazine derivatives If the patient is kept in bed these complaints very troublesome but in case of ambulatory patients they become a difficult especially when patients are engaged in such trades as motor driving etc these are hazardous Use of mild sedatives is sometimes helpful

Reaction	Sulphanilamide	Sulphapyridine	Sulphathiazole	Sulphadiazine	Clinical significance
Nausea vomiting	Occasional	Common	Occasional	Uncommon	If severe discontinue drug
Dizziness and headache	Common	Common	Uncommon	Uncommon	Not serious
Cyanosis	Common early and late	Faint, common early and late	Uncommon	Rare	Not serious
Drug fever	Common (5th to 9th day)	Common (5th to 9th day)	Common (5th to 9th day)	Occasional	If serious discontinue drug
Rashes (dermatitis)	Occasional	Occasional	Occasional	—do—	—do—
Primary or acquired hypersensitivity with fever rashes lymphadenopathy etc	Rare	—do—	—do—	Rare	—do—
Leucopoenia with granulocytopenia	Occasional (early or late)	Occasional (early or late)	Occasional (early or late)	Rare	—do—
Agranulocytosis	Occasional	Occasional	Rare	Very rare	—do—
Aplastic anæmia	Very rare	Very rare	Very rare	—do—	—do—
Purpurea with or without thrombocytopenia	—do—	—do—	—do—	—do—	—do—
Mild hæmolytic anæmia	Not infrequent (early or late)	Not frequent	Not frequent	Not frequent	Not serious
Acute hæmolytic anæmia (occasionally with hæmoglobinuria)	Rare	Very rare	Very rare	Very rare	If serious stop drug Give alkalis transfusion of blood and plasma
Hæmaturia	Doubtful	Common generally early	Common generally early	Occasional	If microscopic, discontinue drug

Reaction	Sulphanilamide	Sulphapyridine	Sulphathiazole	Sulphadiazine	Clinical significance
Anuria with azotaemia	Not reported	Not uncommon (first 10 days)	Not reported (first 10 days)	Common	Stop drug
Acidosis	Occasional	Not reported	Not reported	Not reported	Give alkali
Marked leucocytosis	Rare, generally in presence of hæmolytic anæmia	Rare, generally in presence of hæmolytic anæmia	Not reported	Not reported	Not serious
Injection of sclerae and conjunctivae	Not reported	Reported	Not uncommon, may occur with rash and fever (5th to 9th day)	Rare	May be serious discontinue drug
Arthritis	Not reported	*Not reported*	Occasional	Not reported	
Ocular and or auditory disturbances	Rare	Occasional	Reported	Reported	May be serious discontinue drug
Mental disturbances	Occasional, occur early	Occasional occur early	Rare	Rare	
Neuritis	Very rare	Very rare	Very rare	Very rare	May be serious discontinue drug
Hepatic damage	Occasional early or late	Occasional	Occasional	Not reported	—do—
Jaundice	Rare with acute hæmolytic anæmia or hepatitis	Rare, with acute hæmolytic anæmia or hepatitis	Rare with acute hæmolytic anæmia or hepatitis	Not reported	—do—
Splenomegaly	Occasional	Doubtful	Occasional	Rare	—do—
Psychosis and delerium	Uncommon	Uncommon	Very rare	Very rare	If severe discontinue drug

(b) *Nause* ... monest and most troublesome syr ... It is the result of irritant actic ... to some extent but not entirely There is probably some central action also as vomiting occurs even when the drug is given by injection and may be very severe after comparatively small dosage In most cases vomiting can be mitigated by omitting ... in milk or fruit juice or suspended ... keeping the patient on very light ... the drug may be helpful Sometime five minims of tincture of opium given before each dose prevent it, 50 mgm of nicotinic acid by mouth with each dose may be effective Glucose drinks are useful Proper spacing of individual doses may also be helpful

Vomiting is not an indication for stopping the treatment but if it becomes so severe that the drug cannot be absorbed, sulphonamide may be given parenterally In severe infections if vomiting occurs after sulphapyridine one of the other drugs may be given Replacement of sulphapyridine by sulphanilamide or sulphadiazine may be effective

Diarrhœa sometime occurs after administration of these drugs but is not a serious problem Appetite is generally lost when the drugs are being taken Stomatitis rarely occurs after sulphathiazole

(c) *Effects on the nervous system*—Both the central and peripheral nervous systems may be affected but this is comparatively rare

Central nervous symptoms are, psychosis with delerium delusion, hallucinations loss of memory and encephalomyelitis the last named being a very serious complication due to inflammatory changes in the walls of cerebral vessels It has occurred after small doses and probably is a rare idiosyncracy Polyneuritis optic neuritis blindness aphasia stammering, meningeal signs and convulsions may occur Mental aberrations such as those simulating alcoholic intoxication, diminution of mental acuity, acute psychosis wild delirium and maniacal states have been observed Organic changes in the nervous tissues can only occur with very massive doses in experimental animals

Peripheral neuritis is a rare manifestation and has been observed after use of sulphathiazole in large doses and for prolonged periods The patients generally recover from nerve injury thus produced

(d) *Cyanosis*—It usually appears early in the course of treatment and is

methæmoglobin Though alarming to the patients' relations cyanosis is not of any great significance except in patients who are markedly anæmic and it is not an indication for stopping the drug In severe anæmia and pneumonia it may aggravate the disability by causing anoxæmia The idea that sulphur containing fluids and drugs given concurrently predisposed to cyanosis has been shown to be incorrect

When cyanosis is due to methaemoglobinaemia it can be controlled by methylene blue, which accelerates the conversion of methæmoglobin into hæmoglobin It may be given either by intravenous injections of 1 2 mgm per kilo body weight, as 1 per cent solution (10 to 20 ccm), or by the mouth in

doses of 1 to 2 grains (0.2 gm) when it acts in 3 to 4 hours With this treatment cyanosis rapidly clears up but it may return after 24 hours It can be kept down by giving methylene blue with sulphonamides from the very beginning Methylene blue may however cause vomiting and diarrhœa and when given by injection it is liable to cause tissue necrosis When cyanosis is due to sulphaemoglobinæmia methylene blue has no effect unlike methæmoglobin sulphæmoglobin is not readily convertible into hæmoglobin Marked cyanosis is seen mostly after use of sulphapyridine and sulphanilamide less after sulphathiazole and sulphadiazine derivatives and not at all after sulphaguanidine and succinylsulphathiazole

(e) *Acidosis or ketosis*—This is indicated by hyperpnœa with or without physical exertion and acid urine or in case of ketosis by smell of acetone in the breath drowsiness vomiting and acetone in urine There is reduction of CO_2 [illegible] There is [illegible] liminished [illegible] od due to [illegible] CO_2 into [illegible] ian lamide is essential and even with such concentrations as 3 to 4 mgm per cent patients may experience difficulty when taking strenuous exercise

In such cases large doses of sodium bicarbonate should be given and if ketosis is present glucose or sugar should be administered Acidosis is minimised by giving bicarbonate of soda in doses equal to the drug with each dose but such a practice is not des[illegible] [illegible] lphanilamide sulphapyridine sulphad[illegible] ome degree of acidosis always occ[illegible] e clinically evident The loss of t[illegible] urine and in some cases air hunger may actually be present

(f) *Drug fever*—This occurs during the administration of the drug or within 24 hours after the course has terminated It occurs with all sulphonamides but more frequently when sulphanilamide or sulphathiazole is used than with others but is frequent with sulphamezathine If the drugs are given for the first time it rarely appears before the 7th day of treatment but if previous courses have been given it may appear much earlier even on the 1st day Drug fever may be accompanied by chills severe headache vomiting tachycardia skin erup tions cyanosis and collapse Once an individual has had drug fever it may recur months later following a single small dose of the compound and the succeed ing reaction may be very violent That is the reason why patients are to be questioned about previous doses If fever is produced before six days after the adm inistration of the drugs it is often an indication that other toxic symptoms including skin lesions hæmolytic anæmia etc will occur later If fever is definitely due to the drug it is a warning sign and the treatment should be temporarily stopped Before restarting treatment a small dose of the drug is given and if there is a sharp rise of temperature within 12 hours the case is unsuitable for sulphonamide therapy

The incidence of dr[illegible] 36 per cen[illegible] Temper[illegible] with th[illegible] and clir[illegible] improving Omission of drug brings down the tempera ture but if it does not agranulocytosis should be suspected Para aminobenzoic acid is neither preventive nor curative of this condition

(g) *Skin lesions*—Different kinds of rashes closely resembling exanthematous fevers occur fairly commonly generally associated with drug fever in the course of sulphonamide therapy between 8th and 12th days of treatment The most common rash is a discrete maculo papular measles like eruption distributed over face neck wrists and forearms Urticarial and purpuric rashes have been reported

The distribution of rash and sometimes a history of exposure to light suggest photosensitivity The rash on fading may leave staining and a desquamation Sometimes a finely macular *general roseolar eruption like German measles or a* scarlatiniform rash may be met with The rashes appear late in patients who

has been produced resulting in death

The treatment of these affections is to stop the drug and give large amounts of *fluid the rash often disappears in 24 hours* As the rash may be a *prelude to* serious complications a leucocyte count should be immediately made Patients under sulphonamide therapy should not be exposed to strong sunlight or to x rays during the treatment as they may be photosensitive

Eczematous eruption may rarely follow systemic use but more often after prolonged local use The eruption is at first local but later may spread to other parts especially those exposed to the sun When local treatment is given a *careful watch should therefore be kept Sensitivity to such eruptions when* developed lasts for a long time extending to a year or more Desensitisation is carried out by giving 0 125 gm of the drug twice daily The eruption reaches its maximum on the 5th day and then fades the dose is then doubled If a further reaction occurs the dose is again decreased till eruption fades

(h) *Effects on the blood*—(1) *Leucopænia*—Both production of white and red blood cells may be profoundly affected by these drugs the former being more common and ranging *from slight depression to total absence of granulocytes* Mild degree of leucopoenia is not important unless it rapidly progresses to below

important

2 500 per

immediately

s of fresh

blood are indicated Agranulocytosis occurs both with sulphanilamide and sulphapyridine more commonly with the latter where larger quantities of the

administration or after more than 30 gm of the drug have been ... administration of the drug has to be prolonged beyond seven days a leucocyte count should be done or earlier if large doses have to be given The drug should be stopped if granulocytes fall below 2 000 per cmm If granulopoenia *is not checked* in the early stages symptoms of agranulocytosis develop

often

or may not occur at all ... sore throat cough vomiting and aching pains in the limbs This may be followed by severe septicæmia ulceration of the throat and sometime of the

mouth rectum and vagina This danger can be avoided by having frequent blood counts, and if this is not possible by carefully watching the dosage High total dosage is more likely to cause agranulocytosis than high concentrations in the blood at any time For this reason the drug should not be continued too long and should be stopped if no clinical improvement in the course of the infection is evident If the fever is subsiding and the general condition satis factory after six days of therapy, sulphonamides may be continued for two or three days longer If, however, there is no response in temperature and if other disturbing symptoms are present or in any case if more than fifty tablets have been taken or treatment extended over more than ten days a blood count must be done at once Even a transient leucopoenia may be a sign of a tendency towards depression of bone marrow

Leucopœnia chiefly affecting polymorphonuclears is the essential feature The lymphocytes are at first unaffected but later decrease and the monocytes follow the lymphocytes The total leucocyte count may fall to 50 per cmm Both red cells and hæmoglobin in later stages show a progressive decrease

Treatment—Such decrease of polymorphonuclears on which body immunity is dependent and whose complete absence for seven days is incompatible with life, necessitates swift and drastic action if life is to be saved Blood transfusions should be given at once and injections of liver extract should be given Small exposures to x ray have been advocated Para aminobenzoic acid in doses of 0 3 gm every four hours along with pentanucleotide has been suggested and is said to give better leucocyte response in some cases When severe neutropoenia has occurred once in a patient he should not be given sulphona mides again

Treatment of agranulocytosis is directed to leucopoenia and secondary bacterial infection which is responsible for local pharyngeal lesions often fatal Penta nucleotide is toxic and is not much used now If it is to be used the dose should not exceed 10-20 ccm intramuscularly at least four times a day for four or more days until the leuocytes increase and young forms appear in the blood The best leucopœietic *stimulant is pyridoxine Vitamin B_6 which is issued in 20 mgm tablets* for oral use and 50 mgm ampoules for intravenous use As much as 125 200 mgm are given daily intravenously The symptoms usually subside in 48 hours but the injections should be continued for 5 to 6 days Recovery is heralded by a leukaemoid reaction Folic acid has also been used but it is not so successful as in macrocytic anaemias Glutathione adenine sulphate liver extract yellow liver marrow extract have been tried To deal with secondary bacterial infec tion penicillin is best, sulphonamides should not be used for this

(iii) *Anaemia*—(1) A slowly developing fall in red cells with a drop of 10 to 20 per cent in hæmoglobin is fairly common after sulphonamide drugs have been given for ten days It disappears when these are stopped and is not necessarily a contra indication to continuing treatment

(2) Acute hæmolytic anæmia is a rare but dangerous complication and develops early (2nd to 6th day) It is common with sulphanilamide and occurs more frequently in children and negroes This is due to idiosyncrasy rather than over-dosage and is usually preceded by nausea and headache for about 6 to 12 hours, then follows fever, jaundice, rapidly increasing pallor and shock The liver and spleen are rapidly enlarged, plasma bilirubin is raised and plasma contains hæmoglobin methaemoglobin and methæmalbumin, urobilinogen occurs in urine In some patients the blood may be hæmolysed in one night, hæmo-globinuria may occur, the blood picture shows fall of red cells, leucocytosis

(100 000 per cmm) and reticulocytosis *When such conditions* appear the drug is stopped and blood transfusion should be given immediately, alkalies and large quantities of fluids should be given by mouth or, if this is not possible intravenously as in the *treatment of black water fever, to prevent blockage of* renal tubules with blood pigments

Mortality in this condition is very *high despite active treatment, relapses* occur when the patient appears to be recovering and sulphonamide is given again

Minor degrees of anæmia *not uncommonly* occur *after sulphonamide* therapy and such cases should be treated with iron therapy

(3) In view of the fact that blood transfusions have to be given it should be borne in mind that sulphonamides may produce alterations in blood grouping of an individual This reaction is however, rare

(1) *Anuria haematuria etc*—These are due to blockage of urinary passages by crystalline deposits of less soluble sulphonamides (sulphapyridine sul phathiazole or sulphadiazine and to lesser extent with sulphanilamide) It is liable to occur when the secretion of urine is small owing to deficient intake of fluid or fluid is lost through vomiting or excessive sweating in hot climates It also occurs if large doses of these drugs have been given by the mouth or intra venously and where there is partial obstruction in the urinary tract or toxæmia associated with acidosis is present The site of blockage may be in the renal tubules or in the renal pelvis or ureters This may occur within first 10 days and has been known to occur after 5 to 10 gm of the drug have been given Hæmaturia does not seem to be related to dosage since it has occurred as early as 20 hours after the initial dose or it may be delayed as long as six days In severe cases it may be accompanied by oliguria and followed or preceded by anuria

Briefly renal failure may occur (1) in a acute hæmolytic anæmia (2) by direct toxic effects of the drugs on the kidney, (3) formation of crystals in the kidney resulting in a mechanical interference to the flow of urine

The signs present are pain in the region of the loins radiating to the groin or vague pain in the abdomen There is also diminished output of urine proceed *ing to complete anuria* Hæmaturia *microscopic or macroscopic* should be looked for if oliguria or anuria is present

Prevention—These conditions can be prevented if large quantities of fluids are given (4½ to 6 pints for an adult in 24 hours) to maintain a minimum urinary output of over 1 500 ccm or 52 fluid ounces in 24 hours particularly when *sulphapyridine* sulphathiazole and sulphadiazine are being given The urine should also be kept alkaline to litmus by administration of alkalies If renal pain or macroscopic hæmaturia or oliguria occur the drug should be stopped *immediately and* copious fluids should be given unless there is complete obstruc tion Heat should be applied to the loins by hot water bottles or short wave therapy Generally this gives relief but if anuria persists for 12 hours or if oliguria (less than 500 ccm or 17 ozs per day) persists for 23 hours cystoscopy should be done and a ureteral catheter passed without delay The catheter may encounter gritty obstruction in the ureters The renal pelvis should be irrigated with warm 2 5 per cent sodium bicarbonate solution till the return of flow of urine is clear The catheter should be left in position until urinary function is re-established

In most cases hæmaturia is not a serious symptom and disappears 24 hours after the drug is stopped Sulphonamides should be given with caution in cases of renal impairment

(j) *Effects on the liver* —A few cases of acute yellow atrophy of liver have been recorded after heavy dosage for the treatment of gonorrhœa It has also occurred after sulphanilamide has been placed in the peritoneum after operation Sulphapyridine may remain in liver for 40 days after the drug has been stopped

previous cirrhosis and for this reason sulphonamides should not be prescribed in this condition Hepatitis should be distinguished from jaundice and acute hæmolytic anæmia which occur in the first week

Treatment consists in stopping the drug giving glucose drinks and copious fluids The diet should contain abundant carbohydrates and no fat skimmed milk boiled fish and eggs are given Sulphanilamide has greater toxicity for the live than sulphapyridine and this latter drug is more toxic than sulphathiazole Sulphadiazine has the least toxicity and should be prescribed in all cases where there is impairment of liver function

(k) *Arthritis* —Sudden onset of pain may occur in the larger joints of the body especially after sulphathiazole and the skin over the joint may become red and swollen One or more of the joints may become affected Arthritis usually occurs in cases with fever and dermatitis and it has been mistaken for acute ffering from gonorrhœal guished by the fact that

and r
seve it
discharge burning and itching sensation and injection of blood vessels The eye becomes normal after the drug is stopped Administration of sulphathiazole on later occasions may or may not produce this reaction

(m) *Thrombocytopoenic purpura* is a rare complication Interference with blood grouping has not been definitely established though it is said to have occurred There is no evidence either that administration of these compounds produces any changes in the motility or number of spermatozoa in the semen

Summary of toxic and side effects —

Nausea vomiting diarrhœa stomatitis black tongue pyrexia drug rasnes cyanosis crystalluria hæmaturia oliguria anuria with azotemia acute nephrosis
Mild granul
aplast c anæm
cytopacnia w
d sturbances
les ons in live
inflammatory
with necros s

10. Sulphonamides in Therapy

From point of view of the general practitioner, *the difficulties of sulphonamide* therapy, apart from its value in many conditions he has to treat, must be considered —

(i) To be effective, massive doses have to be given from the beginning *which* are near to *toxic* doses and the medical practitioner who uses these drugs must be prepared to take the risk of discomfort and trouble to the patient accruing *therefrom*

(ii) Doses have to be repeated every 4 to 6 hours day and night if adequate ... blood This ... rrect dose ... rise which ... use of a well equipped laboratory and expert advice with regard to the condition of blood is required

(iii) Apart from their serious toxic effects, the tendency of these drugs is to produce intractable nausea and *often the anxious relatives want the treatment* to be discontinued on this account, which increases the difficulties

(iv) Cyanosis, although not a serious symptom and one which does not indicate discontinuance of treatment, is alarming to the patient and his relatives, especially in cases of pneumonia The patient and his relatives wish to stop treatment with these drugs because they consider it serious

(v) Haphazard treatment with inadequate doses and with interruptions, for such conditions as tonsillitis, common cold, mild cystitis etc, is positively dangerous as there is danger of agranulocytosis and encephlomyelitis occurring leading to fatal results if a patient has idiosyncrasy to the drug

(vi) Ambulatory patients should never be given tablets of these drugs *without explicit instructions* as to dosage and the length of time they are to be taken Many deaths have occurred from overdosage in such cases as gonorrhoea and post mortem examination has shown acute yellow atrophy of the liver, the symptoms preceeding death being intense vomiting, violence, irrationality and coma

(vii) Sulphonamides are very potent drugs and their use should be *reserved for patients in whom the effects can be carefully watched and controlled* Though hospitalization may not be absolutely necessary, the means to counteract *the untoward effects should be at the disposal of the practitioner*

The practitioner *should realise that there is always risk attached to adequate* sulphonamide therapy He should appreciate that *formerly sulphonamide drugs* were the only effective remedies available against bacterial infections With the advent of the even *more effective and practically non toxic antibiotic* penicillin and its availability in sufficient quantities the indications for the use of sulphonamide drugs have been *considerably narrowed down* The sulphonamides need only be used now in infections with organisms either nonsusceptible *to penicillin or* those only slightly sensitive to its action In this connection the development of other antibiotics such as streptomycin and others, which may fill up the hiatus left by penicillin, is awaited with great and ever increasing interest The practitioners should, therefore, make use of penicillin in all cases where it is possible to use it The sulphonamides should only be used when these have to be used (See section on antibiotic)

Complications after sulphonamides occur in 2 5 per cent and mortality rate is 0 2 per cent Some degrees of visceral damage always occur myocarditis has been found post mortem Unpleasant effects such as nausea vomiting headache and depression always occur These drugs therefore should not be used unless there is definite indication They should not be used in ordinary fever or conditions which react to other drugs Sulphonamides should never be given in the treatment of mild complaints as these may produce drug sensitivity which may prove fatal if the drug has to be used for serious disease later Giant urticaria and fatal pulmonary œdema or aplastic anæmia may occur

Overdosage is not common High blood levels such as 180 mgm per cent of sulphathiazole 175 mgm of sulphanilamide 170 mgm of sulphadiazine and 65 mgm of sulphapyridine per cent are required to produce toxic effects in mice Death in man usually results from urinary obstruction from deposition of crystals Undue prolongation of treatment is harmful and gives rise to renal and hepatic damage Seven days treatment is the maximum in a course Toxic hepatitis occurs in the second week and agranulocytosis in the third week If a more prolonged course is required on account of possibility of relapse reduction of dosage for a few days usually prevents this

Drug fever should be differentiated from exacerbation of infection which does not show such accompaniments as eruption vomiting etc Use of sulphathiazole may produce temperature of 106 107°F If sulphonamides have been previously given drug fever may occur within a few hours after the first dose this is likely to occur when the patient has fever and rash previously Such reactions are common with sulphathiazole and sulphadiazine Fever does not occur with sulphathiazole unless the drug has been given for more than seven days When a second course is given 36 per cent get it after a third course 80 per cent

Under dosage is likely to produce resistance of the organism Adequate doses should always be given to produce quick response It is best to follow a high loading dose by a short intensive course

These drugs should not be prescribed to ambulant cases They act better when the patient is resting in bed Rarely acute psychoses develop quite suddenly Dizziness of the head and sensitiveness of the skin to light is common

Sensitisation dermatitis may occur from prolonged and local use Appearance of eczema round the area of use is the first indication It has very rarely occurred after systemic use

The following drugs are likely to produce peripheral neuritis and should not be used —

Sulphanilyl sulphanilamides sulphanyl dimethyl sulphanilamide and methyl sulphathiazole

A combination of sulphonamides with barbiturates before anaesthesia is contra indicated

II Sulphonamides in Infectious Diseases

(1) Streptococcal infections

(a) *Haemolytic streptococcus* —Streptococci have been divided into several groups P hæmolytic streptococcus (Group A Lancefield) is responsible for most of the common infections in man This group is fortunately very sensitive to the action of sulphonamides as also is group C Groups B F G H & K are unsusceptible but they are non pathogenic

The antibacterial action of sulphonamides was first demonstrated in infections with hæmolytic streptococci, and these organisms are amongst the most sensitive to the inhibitory action of the sulphonamide compounds. They are of the greatest value in rapidly spreading lesions where there is little necrosis, e.g. cellulitis, lymphangitis, adenitis and erysipelas. In the two former infections moderate dosage is generally sufficient, and may be gradually diminished after the temperature has been normal for 48 hours. Local collections of pus should be surgically drained and local application of sulphanilamide is helpful. In erysipelas, excellent results have been obtained with sulphanilamide, but it is preferable to employ sulphamezathine on account of its lower toxicity and higher potency. For complications, such as pyæmia, septicæmia or meningitis, sulphathiazole is the drug of choice. The treatment should be started with moderate doses and these may be reduced to half after the temperature falls to normal. For streptococcal dermatitis of the face and ears sulphathiazole wet packs (2 per cent aqueous suspension), or a 5 per cent sulphathiazole ointment have given very good results.

Bacteraemia.—In streptococcal bacteraemia, the use of sulphanilamide has effected great reduction in the mortality and results are even better with the more potent sulphonamides. Sulphathiazole is perhaps the best drug to employ and high blood levels should be maintained till blood cultures remain negative for at least a week. In addition any pus formations should be drained and blood transfusions given if there is any degree of anæmia.

Meningitis.—In meningitis caused by the hæmolytic streptococcus, sulphadiazine is the drug of choice, and intensive dosage should be continued till the temperature has been normal and the spinal fluid sterile for three days; thereafter the dosage may be reduced. The mastoid and cranial sinuses should be investigated for a primary infective focus, and sulphonamides should not be discontinued till such a focus has healed.

Erysipelas.—Sulphamezathine is preferable here on account of its low toxicity and sulphathiazole if such complications as septicaemia, pyaemia or meningitis occur. Dosage required is as for moderate infections and this is reduced to half when the temperature comes down and should be retained at this level for a week. Mortality has been reduced to about a quarter.

Tonsillitis and Rheumatic fever.—Usually tonsillitis is due to streptococcus Group A. Sulphanilamide in doses of 6.0 gm. daily has given good results though this is doubted by many clinicians. Rheumatic fever is associated with streptococcal sore throat though its aetiology is unknown. Prophylactic doses of sulphanilamide reduce incidence of sore throats as well as of rheumatic relapses. The danger of agranulocytosis should however be borne in mind. Sulphadiazine is preferable in this condition because of its slow excretion.

Scarlet fever.—The value of sulphonamides is doubtful unless treatment is started at a very early stage.

Otitis media.—Otitis media should be treated from the beginning as a severe infection and sulphathiazole, sulphadiazine or sulphadimethyl pyrimidine should be given in adults and children in dosage indicated in the table, though it is not necessary to give the first dose intravenously. It is rarely necessary to carry on the treatment beyond 7 to 10 days if rigorous treatment is started from the beginning. All the resistant cases should be treated with penicillin. Sulphonamide or penicillin therapy, however, does not abolish the need for surgical attention and careful local treatment is essential. Careful watch should be kept that drainage is maintained and that the mastoid is not involved.

Pneumonia—In streptococcal pneumonia the sulphonamides have not given such good results as in the case of pneumococcal infections and the incidence of empyema has not been reduced although a reduction in mortality rates has been reported In empyema sulphonamides should be given in high doses and the effusion aspirated frequently If however, there is no improvement after a week s therapy surgical treatment should be considered Penicillin is preferable in such cases

Osteomyelitis—In both acute and chronic osteomyelitis of streptococcal sulphathiazole rmal for 2 or ie sinuses have arly infect on may reappear In chronic cases moderate doses of sulphanilamide are often effect ve

Puerperal fever—In puerperal fever (infection generally A group Lancefield) the best results are usually obta ned with high blood concentrations of sulphan lam de sulphadiazine or sulphathiazole Sulphadiazine is considered by some to be the drug of choice as it is more pleasant to take has a high potency and adequate blood levels can be maintained with less frequent doses The use of sulphonamides has reduced the general mortal ty from puerperal infections from over 25 per cent to less than 5 per cent

Endocarditis etc—In infections such as endocarditis pericarditis arthritis w th pus and brain abscess the best results are obtained if the pus present is first aspirated High blood levels should be maintained for 5 to 7 days and if the cultures are sterile the drug can then be continued at a reduced dosage till the patient has recovered

Subacu e bacterial endocarditis is often due to alpha haemolytic streptococcus wh ch is insensitive to sulphonamides Some cases are due to non hæmolytic group some strains of which are sens tive It may rarely be produced by *H inf uen.ae* or staphylococcus

The sulphonamide drugs have been extensively tried in subacute bacterial endocarditis and on the whole results have not been encouraging It would appear that the low penetration of the sulphonamides through the valvular vegetations is the major difficulty The drug reaches the o ganisms embedded ins de the vegetations in only very low concentrations and the bacteria are thereby enabled to develop a certa n degree of resistance to these drugs There is thus generally an initial response to these drugs the fever subsides and the blood culture becomes negative the organisms however reappear in the blood stream symptoms return and the outcome is generally fatal Recently results w th high dosages of penicillin have given promising results (see sections on antibiotics) and it is likely that the use of sulphonamides in this disease will be g ven up in favour of the more active and less toxic antibiotic agents Should sulphonam des be used very high blood levels should be rapidly attained and maintained [illegible]
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salt should be injected intravenously as the initial dose followed by 1 gm every 4 hours This dosage should be continued for at least 7 days after the spinal fluid has become sterile and then the administration should continue with a reduced dosage for another week

(4) Meningococcal infections

Meningococcal meningitis—The meningococcus is even more susceptible to the action of sulphonamides thai

therapy should be started as soo

zole sulphadiazine or sulphamer

effective Sulphamethazine has

is not recommended Sulphadiazine is the drug of choice in severe cases and the initial dose of 5 gm should be given by the intravenous route Intrathecal injections of the sodium salts of sulphonamide compounds should never be given as they set up irritation In patients who are unconscious or are unable to swallow the drug may be given by the intramuscular route or by continuous subcutaneous drip In such cases liberal amounts of fluids should also be given by the parenteral route to ensure an adequate urinary output

rather with sulphonamides

In fa ie gave better results

than therapy After the

first diagnostic lumbar puncture it is unnecessary to perform further punctures unless there are signs of increased intracranial pressure or the patient does not respond to treatment Penicillin is very effective in the treatment of this disease but as response to sulphonamides is so good penicillin is not generally indicated unless the patient shows signs of intolerance to sulphonamides Penicillin wherever possible should always be given by the intrathecal route

The prophylactic use of sulphonamides in doses of 2 to 3 gm daily for 2 to 3 days has been found to reduce both the incidence of cerebrospinal fever and the carrier rate in epidemics of meningococcal meningitis The mortality rate in this condition has been reduced from 50 to 70 per cent to 1 to 9 per cent

Chronic meningococcal septicaemia responds rapidly to sulphonamide therapy and the temperature comes down on the second day of treatment

Purulent meningitis due to pneumococcus staphylococcus H influenzae etc is generally resistant to sulphonamide treatment Sulphathiazole sulphadiazine or sulphadimethylpyrimidine may however, be given in dosage as required for servere infections, the course should be extended and the initial dose should be given by the intravenous route Frequent examinations of cerebro spinal fluid should be made so that relapses particularly common with *H influenzae* may be detected and treated If penicillin is available it should be given intrathecally as even *H influenzae* is only relatively more resistant to penicillin

(5) Gonococcal infections

Gonorrhoea—The gonococcus is very susceptible to the action of sul

that penicillin should be employed in preference to the sulphonamides not only for the treatment of sulphonamide resistant cases but for all cases of gonorrhœa A comparatively small amount of penicillin given by a few intramuscular injections in a single day, will cure over 90 per cent of all cases of uncomplicated gonorrhœa and the remainder are curable by further penicillin treatment

For the sulphonamide treatment of gonorrhœa sulphathiazole and sulphadiazine are the drugs of choice and suggested dosages for adults are 5 or 6 gm a day given for 5 days Large quantities of bland liquids should be given during this period With such a regime the great majority of cases are rendered non infectious as quickly as possible and there is a minimum amount of subjective discomfort No form of local treatment is necessary in males but in

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due to the presence of a sulphonamide inhibitor in the patient s serum and they respond rapidly and effectively to penicillin therapy

Gonococcal arthritis and gonorrhoeal ophthalmia neonatorum respond well to the sulphonamides For gonococcal arthritis adequate blood levels should be maintained for 1 to 2 weeks and if no response is obtained artificial pyrexial therapy should be combined with the treatment In ophthalmia neonatorum sulphathiazole in doses of 0.25 gm or sulphamezathine 0 15 gm for every 7 pounds body weight should be given 4 hourly for 5 days Local application of sulphonamides does not improve the results and is unnecessary Penicillin applied locally is more effective in these conditions

Vulvo vaginitis of gonococcal orgin in children reacts well to sulphathiazole

Excellent results have been obtained from the use of sulphonamides in the prophylaxis of gonorrhea In a series of 1 000 cases where 4 gm of sulphathiazole were given on the day following exposure only one case developed the disease as against 79 persons in a control group

Non specific urethritis due to hæmolytic streptococci and Bact coli which is communicable may occur, it reacts to sulphonamides It may be borne in mind that it may only be a symptom of a serious lesion in the upper urinary tract

(6) Bact. Coli Infections

In the treatment of Bact coli infections of the urinary tract both methenamine and mandelic acid are useful provided the urine is sufficiently acid but the sulphonamides are effective either in acid or alkaline urine In addition to Bact coli infections the majority of the other organisms responsible for urinary tract infections such as hæmolytic streptococci *Staph aureus, Proteus vulgaris, Aerobacter aerog*

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free from pus after which the dose may be reduced and continued till the urine has remained sterile for three days No undue restriction of the fluid intake should be practiced as besides being dangerous this has no particular advantage

It should be remembered that coliform organisms are *normal intestine* symbionts and are concerned with Vitamin synthesis. The intestinal sulphonamides have remarkable effect on these and after their administration for a week or so deficiencies of riboflavin (B^2), nicotinic acid, thiamine and vitamin K have been observed and a sprue like syndrome may be produced. Black tongue occurring in nicotinamide deficiency has been observed after the use of sulphonamides as well as after oral use of penicillin. The purpuric rash which sometime occurs improves with intramuscular injections of Vitamin K.

(9) Other Infections

Plague.—The protective effect of the sulphonamides against plague were first demonstrated when Durand (1939) found that sulphapyridine could protect mice inoculated *with 10,000 times the fatal dose of pasteurella pestis*. Sokhey and Dikshit (1940) using sulphathiazole cured 85 per cent of mice infected with a fatal inoculum even when treatment was started 48 hours later. They found that this drug was more potent than sulphapyridine and gave as good results as the most potent serum. Wagle, Sokhey, Dikshit and Ganapathy (1941) in a large series of cases of bubonic plague obtained mortality rates of 28 per cent using serum alone, 24 per cent with sulphapyridine and only 15 per cent using sulphathiazole. Even better results have been obtained with a combination of serum and sulphonamide therapy. Sulphathiazole or sulphadiazine should be employed in the treatment of plague in the same dosages employed as for other severe infections. This is combined with streptomycin on the basis of fatal daily dosage of 0.04 gm per kilo divided into 8 parts given intramuscularly day and night.

Haemophilus influenzae infections.—In pneumonia due to *H. influenzae*, the sulphonamides are not of much value but in meningitis due to this organism whereas previously the mortality rates were about 90 per cent in the ordinary age groups and 100 per cent in infants under two years of age, treatment with sulphonamides combined with immune serum has effected remarkable reductions in the mortality from this disease. In a large number of cases so treated the mortality in the ordinary age groups was practically abolished and deaths were almost confined to infants under 8 months of age. Sulphadiazine is recommended to be given in doses of 0.1 gm per kilo initially, a similar dose after 4 hours and then a reduced dosage of 0.1 gm per kilo per day is continued till the spinal fluid has remained sterile for one week. 25 ccm of serum is given intrathecally and 15 to 75 ccm intravenously. Lumbar puncture is required to be performed daily.

Chancroid (Soft sore).—The prophylactic value of the sulphonamides in preventing chancroid in persons experimentally inoculated with virulent cultures of *H. ducreyi* has been demonstrated. Administration of 2.5 to 5 gm of [illegible] lation prevented [illegible] od results were [illegible] Sulphonamide or sulphathiazole ointment was less successful. The administration of 2 gm of sulphathiazole before exposure to risk and twice afterwards was found to reduce the incidence of chancroid from 5.2 to 0.6 per cent.

For the treatment of chancroid, sulphathiazole, sulphadiazine, sulphapyridine or sulphanilamide may be given in doses of 4 gm a day up to a total of 30 gm or till healing occurs. Buboes often subside without surgical treatment and resolution may be aided by *bathing the lesions in warm saline* and applying iodoform powder.

Tuberculosis—Experimental work with the sulphonamides in tuberculosis has given conflicting results Animal experiments largely with guinea pigs inoculated with tubercle bacilli have given negative results in the hands of some investigators while others have reported retardation in the progress of the lesions

Actinomycosis—Rapid response of cases of actinomycosis to therapy with the sulphonamides have been reported by some observers while others have failed to obtain such success Actinomycosis often responds in a striking fashion to

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Diphtheria—Diphtheria does not respond well to sulphonamides and antitoxin should be relied upon for treatment Thomas (1941) however found sulphathiazole snuff to be of value in diphtheria carriers the organisms being eradicated in about 60 per cent of cases

Anthrax—The response of anthrax to sulphonamides is uncertain Gold (1942) in a comparative series of 63 cases treated 21 of these with immune serum alone with a mortality of one and 39 of the cases with sulphonamides alone without a single death He concluded that sulphonamide therapy was an adequate substitute for immune serum and was more effective than neoarsphenamine A combination of penicillin with one of the diazines is more effective

Cutaneous anthrax appears to respond well to the sulphonamides

Tetanus—Sulphonamides appear to have no prophylactic value against tetanus and tetanus anti toxin should always be used where necessary Bliss Hond and Smith (1941) succeeded in controlling experimental tetanus in mice with sulphathiazole and some measure of success has also been obtained in developed human cases of tetanus

Gas gangrene—The most effective prophylactic measure against gas gangrene is early and efficient surgical treatment In wounds which are liable to develop gas gangrene such as extensive lacerations deep penetrating wounds containing contaminated foreign bodies and wounds where primary operation has been delayed sulphathiazole should be applied locally in addition to the administration of serum Small doses of sulphathiazole should also be given internally when gas gangrene has developed The drug should at first be given intravenously and the maximal blood levels should be maintained before surgical interference is attempted Marfanil (amino methyl benzene sulphonamide) is more active than sulphathiazole against *Cl welchii* and is successfully employed for local application to wounds.

Brucella infections—While the brucella organisms are sensitive to the action of sulphonamides in vitro results in cases of human brucellosis have been uncertain and conflicting Initial results showed promise but then relapses were found to occur in most cases Treatment is most effective in acute cases of only a few weeks duration as also in cases with bacteræmia or a high blood agglutination titre Sulphadiazine is the drug of choice as prolonged dosage is usually necessary An initial dose of 4 gm is followed by 1 gm 4 hourly for 10 to 12 days A second course may be given if necessary after an interval of several weeks

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Actinomycosis—Rapid response of cases of actinomycosis to therapy with the sulphonamides have been reported by some observers while others have failed to obtain such success. Actinomycosis often responds in a striking fashion to penicillin treatment and this drug may well prove to be the drug of choice. If it is decided to use sulphonamides one of the more active preparations such as sulphathiazole or sulphadiazine should be employed in high dosages as for severe infections.

Diphtheria—Diphtheria does not respond well to sulphonamides and antitoxin should be relied upon for treatment. Thomas (1941) however found sulphathiazole snuff to be of value in diphtheria carriers the organisms being eradicated in about 60 per cent of cases.

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(10) Rickettsial and Virus Infections

Lymphogranuloma inguinale—Virus infections are not as a rule benefitted by sulphonamides but the virus of lymphogranuloma is susceptible The drug however appears to act in a different way to bacterial infections and the virus appears to persist in the body in an attenuated form As against the normal duration of 6 to 8 weeks in untreated cases in those treated with sulphonamides the adenitis and proctitis clear up in 4 to 5 weeks The Frei test however continues to be positive after cure indicating that the virus still persists in the tissues Sulphadiazine or sulphapyridine are the drugs generally employed in dosages of 5 gm daily for 5 days followed by 3 gm daily for 6 to 12 weeks Proctitis responds well to treatment even when stricture has developed

Granuloma venereum—In this condition antimony treatment combined with sulphonamides gives beneficial results if the disease is not very chronic

Other virus infections—Sulphonamides have no effect on the virus of influenza but as it is often associated with bacterial infections such as streptococci staphylococci etc which are susceptible to sulphonamides it may have some beneficial effect in preventing complications Herpes zoster is not affected by sulphonamides

(11) Affections of the Eye

Conjunctivitis responds well to 2 5 to 10 per cent solution of sodium sulphacetamide instilled at intervals varying from 2 to 8 hours according to the severity of the infection Inclusion conjunctivitis a virus infection which ordinarily runs its course for 4 to 6 months usually heals in 2 to 3 weeks following the use of a 5 per cent sulphathiazole ointment

Corneal ulcers generally respond well and a 20 to 30 per cent solution of sodium sulphacetamide *should be instilled into the eye every 2 hours* in severe cases and at correspondingly less frequent intervals in the less severe infections In infected corneal abrasions such as are commonly seen in miners and industrial workers good results are obtained with the application of sodium sulphacetamide powder after cocainisation of the eye

For blepharitis the application of a 2 5 to 10 per cent sodium sulphacetamide ointment one to four times daily is recommended Sulphathiazole ointment also gives good results Where the use of an ointment is not suitable a 10 to 30 per cent solution of sodium sulphacetamide may be applied as a paint to the eyelash roots after removal of the crusts

In trachoma the sulphonamides appear to exert a powerful beneficial action in the clinical disease the progress of the disease being arrested in about 90 per cent of the cases Complete recovery however is not attained and it appears that the drug acts on the secondary invading organisms rather than on the trachoma virus itself Trachomatous tissues retain their infectivity to monkeys even after several hours soaking in sulphanilamide solutions Sulphanilamide *is recommended in doses of 3 gm daily* for 10 days and then a reduced dosage for a further two weeks A saturated solution of sulphanilamide (0 8 per cent) may also be applied locally several times a day

(12) Otorhinology

The course of acute *otitis media* is generally greatly cut short and the discharge clears up rapidly The disease should be treated from the start as a severe infection and sulphathiazole sulphadiazine or sulphadimethylpyrimidine

should be administered in dosages suitable for severe infections Sulphonamide treatment is rarely required to be continued beyond 7 to 10 days All resistant cases should be given a course of penicillin and indeed many consider it preferable to use penicillin from the start It must however be cautioned that there is a real danger in using sulphonamides indiscriminately in this condition as sometimes progressive lesions in small undrained foci may be obscured and a false sense of security may delay urgent surgical intervention A number of cases have been reported where the patients were rapidly relieved of all symptoms after sulphonamide therapy only to develop brain abscess after a varying latent period

In acute mastoiditis, treatment is on the same general lines as above and surgical interference is frequently rendered unnecessary by the use of sulphonamides in high dosage continued till the post aural swelling and tenderness have disappeared and the discharge markedly diminished Dosage is then continued at a reduced level for a week after all signs of the disease have disappeared

In *chronic mastoiditis* encouraging results have been obtained and after mastoidectomy sulphanilamide or sulphathiazole powder or paste applied locally hastens the healing process

In acute sinusitis sulphonamides have given exceptionally satisfactory results Sulphamezathine or one of the other less toxic compounds should be employed with an initial dose of 4 gm followed by 1 gm every 4 hours till the temperature is normal Thereafter a reduced dosage is continued for another 2 to 3 days If suppuration occurs surgical drainage must be performed

(13) Diseases of the Skin

For a detailed discussion of the value of the sulphonamide compounds in

sulphonamides should be mixed with an oil in water emulsion as this readily mixes with the exudate In dry lesions water in oil emulsions are to be preferred Simple mixtures of the drugs with soft paraffin are not very effective as the drug is not readily liberated High concentrations possess no advantage over low concentrations and are more likely to cause skin sensitivity Sulphanilamide sulphathiazole and sulphadiazine penetrate the skin to about the same extent but sodium sulphacetamide has a much greater penetrating power

Impetigo responds very well to a 5 per cent suspension of sulphathiazole in an oil and water emulsion the lesions resolving in half the time necessary with ammoniated mercury preparations In very severe cases sulphathiazole may be given by mouth as well Drug therapy should not be continued beyond seven days to minimise the liability to drug eruptions Favourable results have also been reported in erysipeloid

The response is also favourable in sycosis barbae infantile eczema eczemoid dermatitis pyoderma gangrenosum pyogenic granulomata and molluscum contagiosum

Dermatitis herpetiformis responds well but only temporarily to sulphapyridine The drug is given in moderate doses for two or three days then stopped and repeated after a week's interval

Both acute and chronic cases of lupus erythematosus may respond to sulphonamides by mouth, but results are very uncertain

In seborrhœic dermatitis and infective eczemoid dermatitis, successful results have been obtained, particularly where streptococcal organisms are present

Wounds—In the concentration of sulphonamides ordinarily achieved in wounds, phagocytosis is not adversely affected, fibroblasts continue to grow at the normal rate and muscular tissue is not injuriously affected Even with very high concentrations, the growth of fibroblasts, macrophages and epithelial cells is only inhibited and is resumed when the drug concentration is lowered Brain tissue is, however, irritated by local application of sulphonamides, especially with sulphathiazole enables the maintenance of adequate concentrations in the affected less irritant and sulphanilamide the least irritant, and the use of these two drugs in small amounts is usually harmless The sulphonamides penetrate from the cavity of the wound into the crevices and deeper tissues Dead tissues are also penetrated, but to a small extent Absorption is more rapid from a recent wound than from an oldstanding wound Absorption is rapid from serous cavities and peritoneal surfaces, but very slight from bony cavities

In practice, equal parts of sulphanilamide and sulphathiazole are used because its solubility ensures rapid penetration and the slow absorption of sulphathiazole enables the maintenance of adequate concentrations in the affected tissues Sulphadiazine possesses low solubility, but has been very sucessfully used in experimental staphylococcal infections of wounds and should be given a trial in suitable cases Marfanil, and a new compound 'V 187 (p-methylsulphonylbenzamidine), are not inhibited by p aminobenzoic acid or by pus, and are specially potent against the clostridia causing gas gangrene They may, therefore, be employed where there is a risk of gas gangrene

In the treatment of fresh wounds, to prevent infection careful preliminary preparation of the wound is of the greatest importance and should be carried out as early as possible All necrotic tissue should be removed, and the wound irrigated with saline solution A mixture of equal parts of sulphanilamide and sulphathiazole in powder in microcrystalline form, is then blown over the raw surface in a thin film with a powder blower, and the wound closed without drainage if possible It is important that the powder should be sterilized before application to avoid risk of introducing spore bearing anaerobes into the wound If local anæsthesia has to be used local anæsthetics such as nupercaine or stovaine which do not inhibit the activity of sulphonamides, should be employed More than 15 gm of the sulphonamides should not be used at one time in a recent wound to avoid the risk of reaching dangerous blood levels The application of the powder is repeated each time the wound is dressed If the risk of sepsis is great, *as in severe lacerations of the muscles or in compound fractures,* oral therapy is given in addition to the local applications

In the field or at first aid posts, or where immediate surgical attention to the wound is not possible, it is best to apply 5 to 15 gm of sulphanilamide powder at once to the wound, or if sterile powder is not handy, 4 gm of sulphadiazine may be given by mouth

In the treatment of suppurating wounds, the local application of sulphonamides is not of any particular value, though Marfanil has been widely used in Germany with success, as its action is not inhibited by the presence of pus and it is also more potent against *Cl welchii* than the other sulphonamides Sulphona

mides administered by mouth are of value in cellulitis lymphangitis or if bacteræmia complicates the wound or when osteomyelitis is also present Sulphathiazole sulphadiazine or sulphamezathine should then be given in moderate to high dosage according to the severity of the case

In the treatment of compound fractures very good results have been obtained following the local instillation of sulphonamide powder and primary closure of the wound Secondary infection does not generally occur union is more rapid and the incidence of osteomyelitis is greatly reduced Good results have also been obtained even in old compound fractures with active infection and sinuses

Burns—For first aid treatment pending removal to a hospital a 3 per cent water soluble sulphanilamide cream should be applied to the affected area *without attempting to clean the wound or removing blisters After the patient has been* conveyed to a hospital shock is treated and the area is cleaned and blisters removed A 10 per cent sulphanilamide cream is then applied to all the burnt areas covered over with gauze or oil silk and left in position for 6 to 10 days after which the cream may be re applied if necessary Alternatively burns on the trunk and limbs are coagulated by a tannic acid jelly containing 5 per cent sulphathiazole or sulphadiazine and the above mentioned sulphanilamide cream applied only to the face hands and genitals A 3 per cent solution of sulphadiazine in 8 per cent ethanolamine has also been used as a spray to produce coagulation Sulphanilamide is also used as dusting powder for wounds This should however, be replaced by wet sulphanilamide packs if after repeated applications a dried crusted surface is produced

In extensive burns not more than 15 gm of sulphonamide should be applied in 24 hours to avoid the danger of excessive absorption The blood concentrations should be estimated at frequent intervals and ample amounts of fluids and alkalis should be given concurrently to avoid toxic symptoms

(14) Miscellaneous Diseases

In tularaemia sulphathiazole in doses of 6 gm daily produced some benefit although the improvement is not dramatic

Malaria—The sulphonamide compounds have been shown to possess a very definite antimalarial action on the plasmodia in both monkey and human malaria P falciparum infections respond better than P vivax and the sulphonamides with mepacrine The sulphonamides are slower in action and are less effective than either quinine or mepacrine and relapse occurs in a very large proportion of the cases Sulphathiazole sulphadiazine sulphadimethylpyrimidine and sulphapyridine are all much more active than sulphanilamide

Amœbic dysentery—The sulphonamides possess no significant activity against the *E histolytica* In cases of amœbic dysentery which do not respond to the ordinary amœbicidal drugs good effects have been reported with a combination of penicillin (total 2 million units) and succinylsulphathiazole (20 gm daily to a total of 80 gm) in suppressing the secondary infection

Filariosis—The sulphonamides have been found to have a beneficial effect on the secondary streptococcal lymphangitis and cellulitis occurring in this disease There is no effect on the filaria Any one of the compounds suitable for use against streptococcal infections may be used in moderate dosage

PART IV

CHAPTER III

ANTIBIOTICS

Penicillin

Other Antibiotics

*PENICILLIN

1 Historical and General

Pasteur and his colleagues (1877) found that certain air borne organism inhibited the growth of anthrax bacillus and were the first to make the suggestior that he phenomenon of antibiosis could possibly be used in the treatment of certain infections This inhibition has now been shown to be due to productior of certain substances which have definite chemical and biologic properties A early as 1899 certain products of *B pyocyaneus* were found useful in the treat ment of anthrax and diphtheria and in 1929 Fleming reported the discovery of penicillin This observer found that around a large colony of contaminating mould the colonies of staphylococci became transparent and underwent lysis This mould belonged to the genus penicillium and he named the antibacterial substance penicillin The mould was later identified as *Penicillium notatum* a species allied to *P Chryogenum (Thom)* It was shown later that broth filtrate containing penicillin possessed remarkable selective antibacterial properties It produced inhibition of growth of a variety of gram positive pathogenic organisms but was relatively ineffective against gram negative organisms such as *Escherichia coli H influenzae* etc Fleming further observed that penicillin filtrate was relatively nontoxic for animals or cellular elements including leukocytes and it was non irritant and non toxic to the conjunctiva

[*In preparation of this Section I gratefully acknowledge the help I have received from Penicillin and its practical application by Sir Alexander Fleming Butterworth & Co Ltd London 1946 and Penicillin its properties uses and preparations the Pharmaceutical Press London 1946]

Chain and Florey (1938) made an intensive survey of such naturally produced antibacterial substances from chemical and biological standpoint and one of the first to be taken up was penicillin They described methods of purification of penicillin and its bacteriostatic properties in vitro and also its chemotherapeutic action in animals mostly using the sodium salt of penicillin One of the chief difficulties was that penicillin was very unstable and sufficient quantities could not be produced for experimental purposes In 1941 they prepared fairly pure penicillin and found that it could retain its potency for months if kept in a refrigerator at 4°C Heating momentarily to 100°C had little effect but after boiling for one hour its potency was lost entirely, heating for half an hour at 55°C did not reduce its potency, but autoclaving destroyed it entirely When administered to the patients penicillin was recovered from the urine of patients showing that it passed through the human body Florey then went to the United States of America and carried on his investigations in collaboration with the workers there The work was then taken up by the American investigators in Pennsylvania and at the Mayo Clinic Clinical trials on an extensive scale were taken up On account of the exigencies of the World War II intensive work was done on penicillin and stable salts were produced for clinical use In 1942 the first patient suffering from meningococcal meningitis was successfully treated with intramuscular and intrathecal injections of penicillin and soon its efficacy in many infections was established

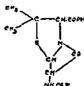
It was first believed that there was only one penicillin but by the method of partition chromatography it was shown that there were at least two if not more By using different strains of *P notatum* and by addition of different organic compounds to the medium on which growth is effected a number of different substances with activity of penicillin have been produced There is therefore a class of penicillins having a similar general structure

2 Chemistry

Chemis

In Great Britain the penicillins so far isolated are named Penicillin I II III and IV and in U.S.A the corresponding penicillins are named F G X and K According to Dale all these penicillins have specific biological action in a high though not quite identical degree and that there are proportional differences still to be explored in their efficiencies against different organisms Penicillin II (G) is predominant in most preparations now in common use

The different penicillins so far examined have the same general structure and vary only in the nature of their side chain R The molecular formula is $C_9 H_{11} O_4 N_2 SR$ The graphic formula has a β lactam ring R varies with different penicillins



Pure penicillin is a rarity but practically pure crystalline sodium and calcium salts are available which are very potent (1600 units per mgm) These are stable and their toxicity is negligible. They can be used in sensitive individuals and also for intra thecal administration and instilling into the conjunctiva

The penicillins are monocarboxylic acids and these are unstable in solution For clinical purposes the sodium salt which is freely soluble in water and gives a stable neutral solution, is generally used at present The carboxyl group can be esterified and several esters have been prepared which are inactive in vitro but in vivo they produce the usual action of

Penicillin breaks up completely by hydrolysis with dilute acids with the production of amino acid $\beta\beta$ dimethylcysteine known as penicillamine *corresponding to d or unnatural* series of amino acids (those isolated from normal proteins belong to g series) Co_2 is also produced during hydrolysis at the same time acylated aminoacetaldehyde The instability of *penicillin in alkaline or alcoholic* solution is due to opening up of β lactum ring with the formation of penicilloic acid derivatives Enzymatic breakdown of penicillin by penicillinase of bacterial origin leads to production of acid.

The structure of the pen cillins is thus relatively simple consisting of two amino acids dimethylcysteine and an acylated series the alcohol c group of which is oxidised *to the aldehyde* The peptide structure is incorporated in B lactam ring There appears to be little hope of commercial synthesis of penicillins at present There is possibility that by modifying the *hydroxybenzyl group in penicillin III add tional pen cillins* may be produced which may be even better than the natural compounds

(1) Physical and Chemical properties of penicillin

The commercial material produced in surface culture plants is mainly penicillin II and the same form is obtained from deep culture plants of the mould used and conditions under which it is grown. *Penicillin produced by some American firms contains penicillin IV* and sodium salt of Penicillin II in pure state

(1) *Salts of penicillin—Free penicillin exists as a strongly* dibasic organic acid and *forms various salts and esters When exposed to air and* when heated both penicillin and its salts rapidly lose their activity Contamination with air bacteria destroys penicillin Free penicillin is very soluble in ether alcohol acetone ethyl acetate amyl acetate, etc It is not so soluble in benzene chloroform and carbon tetrachloride. It is soluble in water *to the extent of 5 mgm per ccm It is very unstable in contact with dilute acids* alkalies, primary alcohols oxidizing agents and heavy metals It is also unstable below $pH_{5\cdot6}$ and above pH_7

Sodium Calcium and other salts Sodium and calcium salts of penicillin are largely used When purified these salts occur in crystalline form the crystals of sodium salt look somewhat *like fence pickets* one end *being pointed and other straight. The calcium salt* contains about 5 6 per cent of calcium The calcium salt unlike the sodium salt is not hygroscopic and it can be stored in the dry state in sealed ampoules for as long as six months at room temperature without any apparent loss of activity Barium potassium magnesium ammonium and silver salts of penicillin have been prepared Barium salt is *stable for an indefinite period in dry state and is a non hygroscopic dry powder*

Methyl ethyl and benzyl esters of penicillin have been prepared These esters are insoluble in neutral or *slightly alkaline* buffers *The esters are soluble in benzene* the aliphatic esters are less active in vitro than penicillin but have considerable activity in vivo probably due to hydrolysis and consequent liberation of penicillin It is possible that they may not be destroyed by gastric juice and possibly some of the higher esters could be administered by mouth

(2) Inactivation of penicillin

Penicillin is inactivated by contact with various heavy metals (copper, lead zinc etc) in a manner which is not understood It is inactivated by such bases as ammonia aniline or quinine in the ionised state

Ethyl alcohol in high concentrations destroys penicillin and therefore should be rigorously excluded There is however no objection to its use to sterilise rubber caps of penicillin vials *Inactivation is due to splitting up of β lactum ring* and formation of ester of penicillinic a [illegible] on the keeping properties of aqueous solutions of [illegible] dly inactivates penicillin and is used for freeing [illegible] substances (*phenol phenoxetol*, etc) chlorobutol (0 5 per cent) [illegible] of deterioration Adrenaline which contains *chlorobutol as preservative* also does the same Oxidising agents such as potassium permangnate hydrogen peroxide should be avoided Thiomersalate rapidly causes inactivation.

Penicillinase an enzyme produced by certain bacteria rapidly inactivates penicillin. Its temperature of maximum activity is 37°C and the optimum pH is 6 5 to 8 Impurities in penicillin retard its action It is curious that staphylococci that become resistant to penicillin in vivo *during treatment* of infection with penicillin develop ability to form penicillinase but not those which become resistant in vitro It may be mentioned that the naturally resistant species of bacteria owe their resistance to their possession of *penicillinase* the enzyme which destroys penicillin

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activity of penicillin

Some samples of rubber tubing both natural and synthetic are liable to inactivate penicillin and repeated sterilisation of rubber increases the rate of inactivation

Penicillin does not reduce Fehling's solution but the colour is changed to green. Slight change may therefore occur in the colour of urine of patients taking penicillin when tested with Fehling's solution or oxidizing agents such as hydrogen peroxide and potassium permanganate which rapidly oxidize penicillin thus producing loss of its activity Penicillin is less sensitive to reducing agents and the reduced material retains its activity

3 Manufacture of Penicillin

(1) The process of manufacture of penicillin may be discussed under the following heads

Preparation of medium—All media now contain Corn Steep liquor' (obtained by steeping maize) which has a substance which stimulates the growth of penicillin The media are generally based on CZAPEK DOX medium and the following is a modification in use that has been found to be satisfactory —

Sodium nitrate ($NaNO_3$) 3 00 gm potassium acid phosphate (KH_2PO_4) 1 00 gm potassium chloride (KCL) 0 50 gm magnesium sulphate ($MgSO_4.7H_2O$) 0 5 gm, ferrous sulphate ($FeSO_4.7H_2O$) 0 01 gm glucose 40 0 gm distilled water q s 1 000 ccm Different investigators have produced different modifications of this medium and some have substituted brown sugar for glucose It was further demonstrated that the presence of zinc

... it has also been shown that ferrous sulphate and potassium phosphate could be reduced The addition of monohydrogen phosphate and dihydrogen phosphate for purposes of buffering the medium is however desirable

Sterilisation and cooling of medium—Sterilizers of special designs are used and for mass cooling of penicillin flasks and special coolers have been designed

Preparation of spore s ... to ensure the purity of the parent c ... ufacturing units Suspensions of spo ... e uniform distribution and a simple ... used The operation is carried out inside a large incubator in some of the large factories with a spray gun Incubation time and temperature depend on each other and on the particular strain used

Deep Fermentation and Harvesting—Here sterilizing cooling inoculation and incubation are all carried out in the same vessel of which batteries are assembled

After incubation the liquid under the mould mycelia is removed from the mould into tanks and broken up mycelia are removed by filtration Great care is taken that bacterial contamination does not occur

Concentration and drying—By suitable adjustment of pH and choice of solvents, and sometime in combination with charcoal adsorption stage a concentration many times the original metabolite solution at harvesting is reached The idea is to produce a concentrate containing about ... per cent of solids suitable for drying The yellow colour of penicillin is due to pigment chrysogen which is a contaminant in the finished product

Drying is done by spray and freeze drying methods, the latter needs a special plant which entails considerable expense This method is similar to that used for drying human plasma in bulk The dried powder is stored and weighed under aseptic conditions The best method of freeze drying is that which involves filling of intended vials with the ... per cent solution and drying it there

During all stages in the process of manufacture very strict supervision by experts is essential Three methods are generally employed for manufacture of penicillin —

Penicillin breaks up completely by hydrolysis with dilute acids with the production of amino-acid $\beta\beta$ dimethylcysteine known as penicillamine, corresponding to d or unnatural series of amino-acids (those isolated from normal proteins belong to g series). CO_2 is also produced during hydrolysis at the same time acylated aminoacetaldehyde. The instability of penicillin in alkaline or alcoholic solution is due to opening up of β lactum ring with the formation of penicilloic acid derivatives. Enzymatic breakdown of penicillin by penicillinase of bacterial origin leads to production of acid.

The structure of the penicillins is thus relatively simple, consisting of two amino-acids, dimethylcysteine and an acylated serine, the alcoholic group of which is oxidised to the aldehyde. The peptide structure is incorporated in B lactam ring. There appears to be little hope of commercial synthesis of penicillins at present. There is possibility that by modifying the hydroxybenzyl group in penicillin-III additional penicillins may be produced which may be even better than the natural compounds.

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(i) [illegible] —Free penicillin exists as a strongly dibasic organic acid and forms various salts and esters. When exposed to air and when heated, both penicillin and its salts rapidly lose their activity. Contamination with air bacteria destroys penicillin. Free penicillin is very soluble in ether, alcohol, acetone, ethyl acetate, amyl acetate, etc. It is not so soluble in benzene, chloroform and carbon tetrachloride. It is soluble in water [illegible] per cent. It is very unstable in contact with dilute acids, alkalies, primary alcohols, oxidising agents and heavy metals. [illegible]

[illegible] salts of penicillin are largely used. When purified these salts occur in crystalline form [illegible] one end being rounded and other straight. [illegible] per cent [illegible] The [illegible] salt [illegible] sodium salt is not hygroscopic and it can be stored in the dry state in sealed ampoules [illegible] as long as six months at room temperature without any [illegible] loss of activity. [illegible] magnesium, aluminium and silver salts of penicillin have been prepared. [illegible] powder.

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(2) Inactivation of penicillin

[illegible]

[illegible]

[illegible]

Traces of substances containing sulphydryl groups such as sodium thioglycolate increase its activity in low concentrations (0·01 per cent) but retard it in higher concentrations (0·5 per cent) An enzyme resembling penicillinase named clarase has been obtained from the mould aspergillus flavus this enzyme is preferable to penicillinase for destroying activity of penicillin

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Sterilisation and cooling of medium—Sterilizers of special designs are used and for mass cooling of penicillin flasks and special coolers have been designed

Preparation of spore suspension and inoculation—Great care has to be taken to ensure the purity of the parent culture from which subcultures are prepared for manufacturing units Suspensions of spore are made with a suitable wetting medium to secure uniform distribution and a simple automatic pipette delivering a constant volume is used. The operation is carried out inside a large incubator in some of the large factories with a spray gun Incubation time and temperature depend on each other and on the particular strain used

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Drying is done by spray and freeze drying methods the latter needs a special plant which entails considerable expense This method is similar to that used for drying human plasma in bulk The dried powder is stored and weighed under aseptic conditions The best method of freeze drying is that which involves filling of intended vials with the 10 per cent solution and drying it there

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During all stages in the process of manufacture very strict supervision by experts is essential Three methods are generally employed for manufacture of penicillin —

(2) *Surface culture method*—Most of the penicillin used in the early studies was produced by the surface culture methods in which the spores of the mould are seeded on *the surface of the culture medium* which is 1 5 to 2 cm in depth Usually 50 ccm of the medium are used in a 200 ccm Erlenmeyer flask, but bottles or even large pans may be used The medium is seeded with spores and the mould is found to grow well at *temperatures between 22°C and 25°C it fails to grow at 37°C* Usually 24 hours after seeding growth begins to appear and on the 3rd day the whole of the surface is covered with a white growth On the fifth day the growth becomes green and somewhat rigid *In the surface cultures the pH of the medium* which starts at 3 5 to 4 5 remains the same for three to four days but as the growth of mould becomes more profuse a rise in pH occurs This is accompanied by rapid development of antibacterial property which reaches its *maximum when the pH approaches the neutral point In order to preserve the* antibacterial titre the mould should be filtered off and the pH of the medium adjusted to 6 5 to 7 The crude broth filtrate is separated and may be kept at icebox temperature without losing its activity *for 7 weeks provided the pH is adjusted to 6 5 to 7* Frozen crude penicillin broth can retain its activity for several months

The advantages of this method are that the yield is fairly high and the equipment necessary is simple A great advantage of growing penicillin by this method is that the individual units are small an [illegible] whole plant Bacterial contamination is a [illegible] ch as *F coli* *B subtilis*, etc , produce enz[illegible] It is there fore very essential that all [illegible]

(3) *Production from submerged cultures*—*This method was largely studied in the* United States Department of Agriculture and also by certain commercial concerns To produce submerged growth it is essential to effect aeration by constant agitation of the *culture This is done by shaking the flasks and by designed aerators rotary drum* fermenters equipped with aerators and agitators are also used Under these circumstances the mould grows as small pellets The advantage of submerged methods is that enormous time and labour are saved The disadvantage *is that when contamination occurs* penicillin produced in the whole batch is lost

(4) *Production of Penicillin on Bran*—This method consists in growing a suitable strain of *P notatum*, on moist bran which is thinly spread in suitable trays the bran being first sterilized and then inoculated with the culture of the mould By this method it is possible to produce as much as 200 to 400 units of penicillin per gram of dried bran after it has been allowed to grow for several days *The penicillin is extracted* by the use of suitable solvents The difficulties of this method are that bran is a very poor conductor of heat and is difficult to sterilize and thus to exclude contamination The other difficulty *is that considerable heat is produced during fermentation which is not easy* to dissipate

[illegible]

Bran [illegible]
one [illegible]
of *P notatum* the inoculated material is shaken and incubated at 24°C [illegible]
this method as much as 150 units of penicillin per gram may be produced (Srinivasa Rao)

(5) *Properties of penicillin*—The stability of penicillin depends on the presence of *moisture* and if this is rigidly excluded penicillin will not lose its activity for a year even without storage in a refrigerator The U S A Food and Drugs Administration require that *the moisture content of crystalline sodium penicillin shall not exceed* 1 0 per cent and that it shall not lose more than 25 per cent of its potency when stored at 100°C for six days The label need not bear any special instruction with regard *to storage* conditions

The sodium salt is highly hygroscopic and the calcium salt least hygroscopic In this connection it should be remembered that rubber plugs which seal the vials are not *entirely* impervious to moisture and even with the aluminium seal and dust cap appreciable amounts of *moisture* may diffuse into the vial and deterioration may begin. Investigations in this connection show that when stored below 10°C and protected from *moisture penicillin* which has been adequately dried will remain active for a year At 37°C dried powder retains its full potency for 60 days

Solutions of the barium salt have maximum stability at pH 5 5 to 7 5, at 2°C for several weeks boiling for 30 minutes renders it inert. Sodium penicillin II in solution *has a max*[illegible] [illegible] its original activity by 50 per cent in 14 days at 24°C.

The effect of temperature on deterioration is less on more purified penicillin than on less purified There is an initial lag in deterioration but once it begins the rate progresses rapidly probably owing to increasing activity of solution as a result of decomposition

Increase in rate of decomposition with rise of temperature is rapid The solutions should therefore be stored in a refrigerator or on ice In cold storage solutions will retain their activity for a week at best

No information is available as yet with regard to the properties of four varieties of penicillins so far identified It is probable that at a reaction near neutrality the activity is appreciably longer

4 Pharmacological Action and Toxic Effects

(1) Absorption and excretion

Subc intra intra route

(1) *Absorption* —Penicillin is readily absorbed and diffuses well into most of the body tissues and fluids When given by the intravenous intramuscular or subcutaneous routes penicillin is readily absorbed and its presence can be determined by various methods Little information is available as to what constitutes an optimum or even an adequate blood level effective in the treatment of various diseases Practical experience has shown that penicillin therapy often produces remarkable effects when penicillin blood level is below the stated effective figures for much of the time as is the case when intermittent injections are being given

Penicillin disappears from the blood quickly after a single intravenous injection although it attains a high concentration for a short time. Given by the subcutaneous route the concentration in the blood is well maintained but detectable amounts are present here for longer periods than after a single intravenous injection After a single intravenous injection the concentration in the blood reaches its highest point and then rapidly falls the peak of concentration depending on the quantities of penicillin administered

The amounts of penicillin sufficient to have inhibitory effect on micro organisms are no longer present three hours after a single injection After intramuscular injection of 50 000 i u of penicillin in a single dose the blood obtained one hour after injection did not contain more than one unit of penicillin per ccm Three hours after injection no penicillin activity could be detected in the blood When continuous intravenous drip method is used the activity of penicillin is more or less maintained at a constant level

Oral and rectal administration Little or no absorption of penicillin occurs if it is given by the oral route under normal conditions This is due to the fact that it is partly inactivated by the hydrochloric acid of the gastric juice and partly by the enzyme penicillinase which is produced by the intestinal flora In patients suffering from pernicious anæmia where there is no acid in the gastric juice

tions of penicillin in the blood can be obtained by giving large quantities of bicarbonate of soda with penicillin The absorption however in this way is very erratic Penicillin can be absorbed from the duodenum and inhibitory concentrations in the blood could be obtained and steadily and persistently maintained by administering penicillin through the duodenal tube Recent work using larger doses such as 50 000 to 100 000 units has shown that therapeutically effective serum levels may be obtained and maintained by oral administration

Potassium salts give higher and more sustained concentrations than the sodium or aluminium salts It is customary to administer such antacids as aluminium hydroxide magnesium trisilicate etc along with the penicillin salt to counter the effect of the gastric juice

When given per rectum little absorption of penicillin occurs on account of its inactivation by the faecal organisms Penicillin can be absorbed and detected in the blood after injection into inflamed cavities such as pleura peritoneum joint cavities or the spinal canal Absorption however is not rapid and it remains at the site of injection for as long as 24 hours It is also absorbed into the blood after its introduction into the bronchi by means of sprays etc

Rapidity of absorption—The ease and rapidity with which penicillin is absorbed are responsible for the difficulty in maintaining constant concentrations of this substance in the body tissues It is therefore necessary to use frequent injections or continuous infusions Efforts have been successfully made to delay the absorption of penicillin from the subcutaneous and intramuscular routes by suspending it in beeswax and oil mixtures (pea nut oil or sesame oil) Recently a compound of penicillin with procaine in a suitable oil base with the addition of aluminium stearate has proved very successful in delaying absorption adequately so that a single dose of 300 000 units maintains effective therapeutic levels for 24 to 48 hours

(ii) *Diffusion of penicillin into tissues*—It has been shown that red blood corpuscles absorb very little penicillin (10 per cent of the amount present in the plasma) No penicillin activity can be demonstrated in cerebrospinal fluid of cats following intravenous injection and the same is the case with man even after intravenous drip method When penicillin is injected by the intrathecal route it remains in the spinal fluid for at least 24 hours 48 hours later no penicillin activity can be detected In infections of the crebrospinal system penicillin should be given by this route at least once in 24 hours to maintain adequate concentrations When the meninges are actually inflamed and also in meningococcal meningitis penicillin is believed to reach the spinal fluid after intravenous injections These findings have not been fully confirmed

No penicillin activity can be detected in tears after systemic administration of therapeutic doses The concentration of penicillin in the vitreous humor and cornea is usually small For treatment of infections of the eye therefore penicillin should be applied locally as well as systemically Small penicillin activity can be demonstrated in the saliva after its systemic administration

Penicillin is not detected in the pancreatic juice after systemic administration though pancreatic tissues may contain some after intramuscular injection of large doses Penicillin diffuses rapidly into the peritoneal cavity and can be detected within five minutes after an intramuscular injection, the concentration rises even higher relatively than in the blood

Penicillin remains in the pleural cavity for a considerable time after its direct introduction Intra pleural injection of penicillin is indicated in the treat ment of infections of the pleura

After systemic administration of penicillin antibacterial amounts reach the fluid of inflamed and normal joints the concentration being the same as that occuring in the blood

If a large amount of penicillin is given by the intravenous drip method to a woman in labour the blood obtained from the umbilical cord after delivery and also from the mother will contain penicillin Penicillin therefore diffuses through the placenta and becomes available to the foetus

Nerv and marr

Penicillin reaches all the tissues of the body with the exception of the central nervous system and the bone marrow at least in some concentration after systemic administration Even after massive injections no penicillin could be detected in these tissues

(iii) *Excretion*—Penicillin is readily excreted by the normal kidneys and can be recovered from the urine of all patients who have received it, 50 to 60 per cent of penicillin given is fairly rapidly excreted by this route After a single intravenous injection the urinary excretion of penicillin is completed within the first hour of its administration Coliform bacteria in the urine produce a rapid loss of penicillin activity especially if the urine is kept at room temperature

Rena

If renal disease or renal failure or urinary suppression is present excretion is delayed and high concentrations of penicillin can be maintained in the blood Attempts have been made to maintain the concentration of penicillin in the blood by depressing the kidney function by addition of diodrast to the material for intravenous injection Administration of para aminohippuric acid to experimental animals to which penicillin was being given reduced considerably the renal excretion and enabled maintenance of higher level in the plasma

Li e

Penicillin is excreted in the bile of animals after intravenous injections Appreciable amounts of penicillin reach the liver after systemic administration

(2) Toxic effects

The toxicity of penicillin to the mammals is very low in contrast to its toxic effects on bacteria Fleming by rapid successive intravenous injections raised its concentration in blood 1 000 times greater than that required for therapeutic purposes without untoward effects In ambulatory cases of syphilis enormous quantities have been given without harm The purer the penicillin the less its toxicity in fact it has been claimed that penicillin of good quality has no toxicity

The toxicity of penicillin salts of great purity is due entirely to the cation (Na Ca Li etc) The calcium salt is six times more toxic than sodium salt but this would only come into evidence in man of 60 kilo bodyweight after 10 millions units are given

(i) *Toxicity to animals*—As purification of penicillin has progressed the lethal dose for mice has increased The lethal dose of products manufactured by various manufacturers varies widely It has been shown that guinea pigs are particularly sensitive to the toxic action of penicillin It is possible that penicillin destroys the normal bacterial intestinal flora in these animals which is predominently gram positive and in this way interferes with the metabolism of certain substances as are essential for the health of this animal

Toxicity in man—Toxic effects are few and of a minor nature and no damaging effects on the liver lungs kidneys bone marrow nervous tissue etc have been observed even with very massive dosage

The most sensitive tissue to inferior quality of penicillin is the nervous system and meningeal irritation (with cerebrospinal fluid pleocytosis) occurs after intrathecal injections Excessive doses may damage the brain and spinal cord and convulsions have occurred after injection into the lateral ventricles

Thrombophlebitis may occur after continuous intravenous transfusion needing a frequent change of vein certain batches may cause fever urticaria and local reactions but these are due to impurities as also are such reactions as meningeal irritation after intrathecal use Sensitisation phenomena such as urticaria and dermatitis following local application rarely occur

(ii) *Toxic symptoms in man*

Local and general reactions—It has been shown that penicillin sometimes produces toxic reactions both in animals and man —

(1) Pain of a stinging nature at the site of injection usually occurs and brands of penicillin vary in their tendency to produce this pain It is probably not due to penicillin but to associated substances The pain after injection passes off in few seconds A dull pain may remain at the site for half an hour or so and the part may remain tender for 24 hours This may be sufficient to worry some patients and make them dread the treatment To minimise the pain the *drug should be dissolved in very small quantities of saline solution to prevent* larger quantities producing mechanical distention of muscle fibres and consequent irritation

(2) Venous irritation at the site of injection frequently occurs (in 5 to 10 per cent) specially if penicillin contains impurities If this occurs the site of injection should be at once changed Veins of the arm are preferably used for injection because if thrombosis occurs in the veins of the leg embolism may follow

(3) Fever and chills are due to the presence of pyrogens and improperly sterilised apparatus used for injection Since pyrogen free penicillin is now available these are not often encountered Any bacterial contamination with water organisms may produce chills Fever and chills occur in 5 to 10 per cent of cases

(4) Urticaria has been known to occur following local or systemic use of penicillin It may occur later in the course of treatment even after penicillin has been discontinued for a week or more Urticaria when it occurs can be controlled with adrenaline and calcium

(5) Incidence of delayed serum reactions after penicillin is low being no greater than 1 in 1 500 to 1 in 2 000
ance severe malaise mild fever se
effusion into joints exfoliative derm
course of 7 to 10 days Everything p
fraction in susceptible individuals

Subcutaneous type of reactions such as pruritis urticaria toxic erythemas vescicular and bullous dermatitis of hands and feet herpes simplex pityriasis roseoform dermatitis and varying degrees of contact dermatitis and even exfoliative dermatitis have been observed Contact dermatitis may occur after local application of ointments of penicillin Patch test with penicillin is often positive in such patients Positive intracutaneous and scratch test however do not necessarily show sensitiveness to penicillin

Abdominal pains—Patients receiving penicillin sometimes get colicky pains which may be mistaken for appendicitis Besides the above, mild headaches flushing of the face and muscular pains have been met with after administration of penicillin Diarrhaea nausea and vomiting may occur

Uterine reactions—It has been shown that penicillin may stimulate bleeding
A number
undergo
ation *may*

Deficiency of nicotinamide may occur after oral administration and produce black tongue.

(iii) *Toxic reactions of penicillin*

These are grouped by Morginson (1946) into —

pyrogens or other products For practical purposes the possibilities of penicillin as a direct toxic agent are negligible except perhaps with intrathecal use

(b) *Antigen*—Commercial penicillin and crystalline penicillin possess definite antigenic

are usually mild of low incidence and transient

(c) *Therapeutic shock or Herxheimer reaction occurs* after the use of penicillin in the treatment of syphilis Cutaneous reactions occur after 8-12 hours or may be delayed

(d) *Indirect healing action*—On pathological processes producing "therapeutic paradox" of Stokes may occur on account of deforming sclerosis in such arteries as the coronaries which occurs so rapidly that compensation does not take place Rapid healing fibrosis may occur in the liver producing obstruction of portal circulation

(e) *Reaction following intrathecal use*—Penicillin is believed to have direct irritant actions on the centr
than in impurities
and intraventricular
ats dogs and mon
occur with high dos
when ind cated Su
thready pulse stiff neck convulsions and coma Important factors in producing toxic reactions are —(i) concentration of penicillin in solution (ii) slow diffusion of spinal fluid (iii) size of individual doses (iv) and frequency of injections

Penicillin has very low cytotoxicity and even in 1 in 1 000 dilutions the leucocytes of man remain active for at least three hours In antibacterial amounts it does not interfere with the growth and migration of tissue elements such as lymphocytes and fibroblasts or macrophages This is quite in contrast to sulphonamide drugs In fact patients with low leukocyte count and symptoms of agranulocytosis following sulphonamides have improved with penicillin treatment and for this reason it has been used in the treatment of this condition

All the toxic reactions above mentioned are easily controlled and none of these endanger life

5 Antibacterial Activity in Vitro

(1) *Selective antibacterial action*—One of the most important properties of penicillin is its selective antibacterial activity Its action is weak against most gram negative pathogenic organisms while gram positive pathogenic organisms are readily susceptible to its action, even some of the important gram negative organisms are not resistant Fleming showed that an inhibitory effect occurs against various *staphylococci*, *Diplococcus pneumoniae*, *Str pyogenes*, *Neiss*

Gram pi and gra organism

gonorrhoeae, *Neiss intracellularis* and *Corynebacterium diptheriae* It has some inhibitory action on *B anthracis* Penicillin was relatively ineffective against colon typhoid group *B pyocyaneus (Pseudomonas aeruginosa, Proteus vulgaris* and *Vibrio comma*, Enterococci, *Klebseilla pneumoniae*, (Friedlander's bacillus) and *Hemophilus influenzae* were also insensitive On account of these properties penicillin is used to isolate insensitive bacteria from a large number of sensitive organisms It is also used for demonstration of bacterial inhibition and for treatment of infections with sensitive organisms

A list of organisms sensitive and insensitive to penicillin is given in page (636) It has, however, been shown that certain *pathogenic organisms* may be insensitive on the basis of studies made in vitro, and yet penicillin has been found to be effective in vivo in the control of infections produced by some of these *micro organisms*

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Factors influencing antibacterial action —Some strains of pneumococci and *Str viridans* tested were less sensitive than others of the same species These variations are of practical importance as they are responsible for varying responses to the treatment with penicillin in different cases of sub acute bacterial endocarditis *On the whole staphylococci appear to be more uniform in their sensitivity* than streptococci

The *number of organisms initially inoculated affects the activity of penicillin* The pH of the medium is also of importance in connection with the bacteriostatic action of penicillin and a pH from 7 to 5 5 enhances the bacteriostatic action of penicillin

(2) *Inhibitors of penicillin*—*E coli* produces an enzyme like substance '*penicillinase*' *which completely inhibits the action of penicillin* This *substance* is intracellular since it is not found in filtrate of cultures of this organisms The enzyme which inhibits penicillin is also found in certain organisms which are sensitive to the action of *penicillin* and *therefore is not the sole factor* which determines antibacterial action of penicillin against those organisms Bacteria which produce "penicillinase', however, are not likely to be very susceptible to penicillin The living culture the culture filtrates and dried preparations of para colon organisms all destroy penicillin

6 Mode of Action

(1) *Bacter* [illegible] —Penicillin can act as a bacteriostatic o[illegible] present When these are favourable [illegible]rful bactericide The *bacterial cells enlarge the chromosomes begin the process of division* but it is not completed which results in the swelling of the cell This view, however, is not tenable It is believed that penicillin interferes with some vital functions of the early bacterial development and thus has a *bactericidal effect even before* actual cell division occurs It is possibly an inhibitory effect on enzyme action concerned in metabolism of nucleotides

With regard to reaction with sulphydryl groups the effect of penicillin probably resembles sulphonamides but the manner in which it is achieved is different Whereas penicillin may react on sulphydryl groups *in the bacterial* cell the sulphonamides act by interfering with the absorption of an essential nutrient The activity of penicillin is not affected by the number of bacteria present whereas sulphonamides are much less effective if *infection is heavy*

In exceedingly small concentrations penicillin stimulates bacterial growth.

Penicillin kills bacteria in most of the cultures containing *Diplococcus pneumoniae, Str pyogenes* and *Staph aureus* The presence of inactivitated serum frequently reduces the activity of penicillin It has been found that, within certain limits, the rate of killing increases with increasing concentiations of penicillin Penicillin appears to be most effective when active multiplication of bacteria is taking place

Considerable time is necessary for penicillin to act on certain bacteria and bacterial inhibition is not complete unless it remains in contact with the organism for sometime, between 4 to 6 hours If, therefore, penicillin is to be used as a local agent it must remain in contact with the organisms for a considerable time, merely irrigating the surface is not likely to do much good

(2) *Changes produced in Bacteria and Tumor cells*—When *Cl welchii* is brought in *Mor cha*

not explain the antibacterial activity of penicillin Morphologic changes in coccal forms have been observed in the blood of patients receiving penicillin intravenously Gonococci found in the urethral discharges of patients become swollen and irregular in shape two to three hours after administration of penicillin. Morphologic changes also occur in *Staph aureus* cultured in penicillin broth

Certain types of malignant cells may be affected by the action of penicillin *e g* mice sarcoma cells When cultures of these malignant cells are damaged by penicillin they are unable to produce tumours in rats by implantation

(3) *Persisters*—It is known that complete sterilisation is not usually obtained with penicillin and while 99 per cent of sensitive bacteria may be killed a few remain unaffected These are called persisters' and it has been suggested that this is due to the fact that such organisms are dormant and in a non dividing phase. Under suitable condition they resume normal division and are then susceptible to penicillin This may explain difficulty of curing such conditions as bacterial endocarditis

Resistance to penicillin—The position with regard to development of *Pen fast*

accomplished in case of organisms such as *Diplococcus pneumonia, Str pyogenes,* etc As the resistance to penicillin increases, virulence of the organisms declines When staphylococci are allowed to become resistant to penicillin they are said to become many times more susceptible to the antibacterial action of human blood

The question of development of resistance to penicillin is of fundamental importance It is believed that although resistance on the part of the causative organisms may develop among patients who are under treatment, it does not always account for the poor therapeutic results obtained with penicillin in infections with different pathogenic organisms

7 Antibacterial Activity in Vivo

(1) *Animal experiments*—Penicillin was first used in the treatment of infections in vivo in 1940 the mouse being used as an experimental animal Mice can be completely protected by subcutaneous administration of penicillin when these animals have been given 10 000 to a 100 000 lethal doses of *Staph aureus* intraperitoneally The treatment was begun immediately after the bacterial inoculation and penicillin was given every three hours night and day for five days A dose of 4 0 mgm of sulphathiazole per day was required as compared with one mgm of penicillin to afford similar protection Ulceration of cornea produced in the eye of rabbits by using virulent strains of staphylococci was treated locally with penicillin every hour starting one hour after inoculation and continued for 48 hours There are definite beneficial effects on the development of these lesions following local application Beneficial effects of sulphadiazine on such infected eyes were very much weaker than those produced with penicillin Mortality was considerably reduced when penicillin was injected intrathecally into mice in whom meningitis had been produced with *Staph aureus*

Development of resistance to sulphonamides does not interfere with the activity of penicillin Penicillin protects mice even when given six to seven hours after inoculation which is not the case with sulphonamides

Anaerobic infections—Mice infected with lethal doses of *Cl welchii* were successfully treated with penicillin and the infection was controlled Whereas sulphadiazine and sulphathiazole would protect approximately half of the animals infected with this organism penicillin cured 98 per cent of infected animals provided it was given at the same time as infection If however three hours elapsed between inoculation and beginning of treatment decrease in survival rate resulted It has been shown that rather larger amounts of penicillin are required in the treatment of anaerobic infections than aerobic ones Penicillin is effective in infections due to organisms associated with gas gangrene Experimental work shows that penicillin has no neutralizing effect against toxins produced by these organisms It is therefore advisable to combine penicillin therapy with antitoxin in the treatment of established infections

It has been shown that *B anthracis* is fairly sensitive to the action of penicillin In mice who were given 10 000 lethal doses of *B anthracis* and 16 hours were allowed to elapse before the commencement of treatment with 1 000 units of penicillin every four hours more than half of the animals survived

Until the discovery of penicillin no form of treatment except administration of sera was effective in the treatment of erysipeloid disease in man sulphonamides being entirely useless Penicillin is effective in *in vivo* experiments against this disease in animals and these results justify the speculation that it may prove effective in the treatment of this disease in man

Corynebacterium diphtheriae is sensitive to penicillin *Mycobacterium tuberculosis* is insensitive and so are protozoal organisms

Spirochaetal infections—It has been shown that penicillin has a definite spirochætostatic action In rabbits experimentally infected with syphilis penicillin showed some spirochæticidal activity and exerted some prophylactic action also sometime chancres developed late and the lesions were smaller than usual It

was also shown that the strains of spirochaetes in rabbits which received insufficient amounts of penicillin became more resistant to the action of penicillin than the original strain The practical significance of these findings is far reaching Although the action of penicillin against spirochaetes of syphilis in vitro is relatively feeble its action in vivo appears to be powerful

Sp recurrentis and leptospira infections—The blood of mice infected with strains of spirochæte of relapsing fever (*sp recurrentis*) could be cleared of spirochætes within 24 hours by subcutaneous injection of 250 units of penicillin Inoculation of the blood from treated animals into fresh mice did not convey the infection Although *Leptospira icterohæmorrhagiæ* was insensitive to the action of penicillin in vitro yet it is effective *in vivo* and it is likely that penicillin might be of value in the treatment of Weil s disease

Spirillum minus—Rat bite fever is associated with *Spirillum minus* or *Streptobacillus moniliformis* In the former condition organic arsenical preparations are of some value but not with the infection of the latter organism although gold preparations have some effect Penicillin given intravenously 15 minutes after inoculation of the animal with *Spirillum minus* prevented the development of the disease Penicillin is said to be more effective than neoarsphenamine and produces complete inhibition of growth of *Streptobacillus moniliformis* in vitro in the presence of 0 1 unit of penicillin per ccm and partial inhibition with 0 01 unit per ccm

Virus and Rickettsial infections—It is well known that no therapeutic agent is of much value in the treatment of infections produced by virus of ornithosis and penicillin failed to completely eliminate the virus from the bodies of the treated mice Protective effects however were obtained against these usually fatal infections

Penicillin also exerts an inhibitory action on the multiplication of Rickettsia which produces murine typhus The virus of lymphogranuloma venereum is resistant to the action of penicillin (Andrews) This virus as well as trachoma virus are acted upon by sulphonamides

The handicaps of chemotherapy of virus infections are known and many [illegible] Sulphonamides are however effective [illegible] granuloma venereum and trachoma and [illegible] virostatic activity against some of the [illegible]st most of the small viruses penicillin has little or no activity

(2) *Sensitivity of organisms*

In the following list the names of organisms sensitive and insensitive to [illegible]

[illegible] of the infective organisms and the concentration of penicillin at the site of infection

The extraordinary minute quantities of penicillin required to inhibit the growth of bacteria may be judged from the fact that concentration of 0 13 unit per ccm (equivalent to about 1 in 13 000 000) is lethal to most strains of meningococcus 500 units per mgm completely inhibit the growth of staphylococcus at dilutions of 1 in 30 000 000 and partial inhibition was produced with dilutions up to 1 in 160 000 000 (one gram in 2 000 gallons) In most of the clinical infections the effective blood level is 0 4 units per ccm equivalent to 1 in 16 000 000

(i) *Methods of determination* —The methods depend on the measurement of zone of inhibition when the test organism is streaked on an agar plate containing a depot of penicillin Growth is inhibited on an area surrounding the penicillin depot the extent of this area showing the sensitivity of the organism Fleming's gutter plate method consists of making a gutter by removing a strip of agar from the plate The gutter is then filled with melted agar in which penicillin has been incorporated The infecting organisms and the standard organism are streaked from the gutter to the edge of the plate, which is then incubated The length along which the growth takes place is in inverse proportion to the sensitivity of the organism Filter paper soaked in penicillin may be put in the gutter instead of melted agar with penicillin

(ii) The following table gives the organisms which are susceptible and those which are insusceptible to penicillin in vivo and in vitro —

Sensitive

Staphylococcus (albus aureus)
Streptococcus (pyogenes viridans anærobic non hæmolytic)
Pneumococcus (*Diplococcus pneumoniae*)
Gonococcus (*Niss gonnorrhoea*)
Meningococcus (*Niss intracellularis*)
B anthracis
Diphtheria group
Clostridia (tetani novyi perfringes histolyticus œdematis maligni botulinum)
Streptobacillus moniliformis
Actinomyces
Spirochætes (relapsing fever syphilis yaws vincents angina Weils disease)
Spirillum minus (rat bite fever)
Larger viruses (psittacosis ornithosis) partly
Rickettsia partly
Besides these *B subtilis* (hay bacillus) *Streptobacillus moniliformis Erysipellothrix rhusiopathiae* (erysipelodi swine erysipelas) sarcina

Insensitive

Enterococcus (str fæcalis)
Non pathogenic gram negative cocci
Typhoid paratyphoid group
Dysentery group coli group
Vibrio choleræ
Proteus vulgaris
Pastuerrella (pestis tularensis)
Pseudomonas group (Ps æroginosa B fluorescense ducreyi)
Hæmophilus group (influenzæ pertussis)
Acid fast group (tubercle smegma)
Brucella melitensis
Friedlander's bacillus (Klebsiella pneumoniæ)
Plasmodium vivax
Most of the viruses
Trypanosomes
Besides these yeasts monilia moulds etc

8 Penicillin in Therapeutics

Fleming (1946) has laid down a few simple rules for penicillin treatment —

(1) Penicillin should only be used when the infecting organism is sensitive to it

(2) Among the sensitive organisms there are some strains which are relatively less sensitive than others but in most cases the line of action is quite clear Infection with sensitive organisms are controlled while those with insensitive ones generally [illegible] Treatment however, [illegible] s established any more [illegible] of diphtheria

(3) Penicillin must come in contact with the organism by local treatment or through the circulation

(4) The dose should be such that the concentration of penicillin attained should be sufficient to destroy bacteria and that this concentration should be maintained

(5) The treatment should be persisted until the infection is controlled

Concentration in blood—On account of rapid excretion of penicillin its concentration in the blood and tissues rapidly falls The following table shows concentration attained in serum during treatment with repeated intramuscular injections —

SERUM TITRE IN UNITS PER CCM

Dose	½ hour	1 hour	1½ hours	2 hours
25 000	0 35	0 2	0 063	0 03
50,000	1 0	0 6	0 3	0 2
100 000	1 7	0 8	0 625	0 3

With continuous intravenous infusion 0 1 unit serum level per ccm is attained for each 100 000 units given per day The same concentration is obtained with intramuscular drip

9 Mode of Administration

(1) *Local*—It was originally observed that local applications of crude broth filtrates of cultures of *P notatum* were beneficial in infected wounds Purified preparations in form of sodium or calcium salts were then used for local treatment and the calcium salt was found to be more satisfactory Physiological saline or water solution containing 1 000 units of penicillin per ccm are suitable for local application and may be instilled through small rubber tubes into deep wounds Higher concentrations should be used for infections with the less susceptible organisms It is important to realize that solutions of penicillin should not be used merely for irrigation but should be instilled because in the former case the drug does not stay in contact with the infected wound long enough to permit bacteriostatic action Injection into an abscess cavity after removing as much pus as possible is a good method of treatment If pus is too viscid to pass through a needle it becomes liquified after one or two days of penicillin treatment Infiltration of penicillin in strength of 1 000 units or more round an abscess sets up a barrier between the infected area and normal tissues and is useful In such cases to prevent pain due to stretching a local anæsthetic is combined with penicillin Local sprays and wet dressings are also useful for surface lesions

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Penicillin is locally applied to serous cavities and the meninges effectively It has been shown that 25 mega units as injected into the blood produce the same effects as 500-1000 units given directly into the theca

Penicillin can be ground with sulphonamides in a mortar in form of a powder each gram containing 5 000 Oxford units A cream with lanette wax as base containing 1 000 units of penicillin per gram is also used for local application Such a cream has been found to be very useful in the treatment of such minor conditions as superficial wounds, minor burns sycosis barbae,

impetigo, etc The cream may be applied directly, but it is better to use it spread thinly on a gauze *In the treatment of severe inflammatory lesions, however,* satisfactory results are more likely to be obtained by a combination of local use with systemic therapy

Local treatment with sprays or inhalations with masks has been successfully used in the treatment of lung conditions By means of atomizers in which a jet of oxygen is led through the solution of penicillin to the patient who inhales it through a mask, the rate of flow can be controlled through a tap The vapour is filtered free of larger particles and the patient inspires through the nose and expires through the mouth In this way doses of 100,000 to 500,000 units dissolved in 3 ccm of water will be absorbed in half an hour Lamellae are used *for eyes and lozenges for infections of the mouth and throat Dental cones* are also used for insertion into the cavity after tooth extractions as a prophylactic measure and for the treatment of dry sockets Each cone should contain not less than 500 units and may also contain sulphathiazole or sulphanilamide

(2) *Subcutaneous route*—This route was not used because the impurity in penicillin solution not only produced considerable pain and discomfort to the patient but irregular absorption Now that purer preparations are available this method is coming into vogue

(3) *Intramuscular route*—Penicillin can be administered by various methods

(i) *Intermittent method*—Twenty thousand units or more in one to two ccm of isotonic saline or redistilled water are given intramuscularly every two to three hours, a standard 22 gauge intramuscular needle, 2½ (6 cm) inches long being used Local irritation sometime occurs but this is not serious, the only disadvantage is that eight injections are required in 24 hours Besides this the concentration of penicillin in the blood shows a sharp rise in the first hour following the injection and then falls low before the next injection is made This is not desirable particularly in the treatment of severe infections

The dose to be given is contained in 1 [illegible]
up in a 2 ccm syringe If necessary 0 5 cc [illegible]
to stop pain when it worries the patient [illegible]
sites In the buttock *the upper and outer quadrant of the gluteal muscle, along* a line joining the top of natal cleft and top of the great trochanter is best In the thigh inject over the great trochanter where there is a lymph space or into the vastus lateralis muscle which has no important structures underneath Injection may also be given in the shoulder into the deltoid or triceps muscles

(ii) *Continuous or intramuscular drip method*—The object is to avoid [illegible] 100,000 [illegible] or more dissolved in a litre may be used, but [illegible] physiologi- [illegible] the needle [illegible] position in the muscle substance

Various types of apparatus have been devised for this purpose, Broadbent type, Edwards type and Eudrip apparatus being examples Some of these are mechanically operated either by electric or clockwork devices A constant level *of penicillin concentration in the blood* is maintained by this method The only disadvantage is that local irritation may be set up and an abscess may form

Intramuscular drip is best given in the outer aspect of the thigh; this allows the patient considerable freedom of movement and the apparatus is available for inspection, to see that the tubing is protected from weight A cradle is helpful and the tubing is led from its bottom

Continuous administration has the disadvantage that it needs a somewhat complicated apparatus and the patient has to be permanently fixed to it. Hospitalisation is essential for this. Intermittent injections can be easily given and inspite of eight injections required in 24 hours, it is preferred. By increasing the dose of penicillin the interval between injections can be increased. The following table after Howard Hugh (1946) gives the dosage required with increasing time intervals —

Time in hours	Aqueous solution (units)	Preparations Oil & Wax suspension (units)
3	15 000	
4	30 000	
6	100 000	50 000*
8	150 000	100 000
10	200,000	120 000
12	300 000	150 000
18	500 000	250 000
24		300 000

The prolongation of effect of penicillin can be obtained by mixing it with such substances as beeswax, peanut oil, etc or with the use of procaine penicillin.

(iii) *Beeswax oil suspensions* —Beeswax has been known to prolong the action of histamine, heparin etc. It was found that if penicillin is combined in this material adequate concentrations of penicillin could be maintained in the blood of experimental animals for 6 to 12 hours and in man for 6 to 7 hours; penicillin was present in the urine for 20 to 30 hours. Mixtures containing 3 to 6 per cent of beeswax in peanut oil have been used for this purpose and assayable blood level was obtained for 7½ hours. In this way it is said a complete course of treatment can be given in an effective manner. Another advantage is that these mixtures even when kept at room temperature for as long as 62 days do not lose their potency. Calcium salt of penicillin is used for preparations of these mixtures and beeswax sesame oil mixtures are even better. This combination should not be mixed with animal oils as a vehicle for penicillin as it is likely to form swellings after intramuscular injections.

Beeswax oil suspension is, however, not suitable when high concentrations of penicillin are quickly required in the blood for severe infections, septicaemia etc. Besides the results of absorption from this type of injection have been shown to be liable to considerable variations which make choice of dosage difficult.

(iv) *Procaine penicillins*. Procaine-penicillin G is a stable crystalline salt obtained by double decomposition of sodium penicillin and procaine hydrochloride and was first described by Sullivan et al (1948). The compound is only very [illegible] 40 i.u. per mgm. It can [illegible] r needle and is painless [illegible] i water, a suspension in [illegible] of aluminium stearate. With suspensions in oil or water, a single dose of 300 000 units is capable of maintaining therapeutically effective levels for from 20 to 24 hours or longer [illegible] 16 hours and in a smaller percentage for even 3 days. It is thus evident that procaine penicillin

G in oily suspension with aluminium stearate is a highly suitable preparation for clinical use and gives slow absorption economy in dosage and prolonged therapeutic blood penicillin levels

Local cold applications—It has been shown that if cold is applied by means of an ice bag at the site of intramuscular injections effective concentrations in the blood can be maintained for 5 hours as compared with 2½ hours without chilling after a single dose The frequency of penicillin injections can in this way be reduced to 2 or 3 instead of 8 or more in 24 hours

(4) *Intravenous route*

Intermittent method—Penicillin disappears from the blood stream more rapidly after a single intravenous injection than after a single intramuscular injection Besides if this method is used a vein will have to be punctured 3 times each day This method therefore is not convenient ordinarily for routine use However the initially high concentrations obtained with intravenous injections makes the method extremely useful in the initial treatment of all such severe infections which carry a high mortality rate

Intravenous drip—The dose of penicillin required for 24 hours is dissolved in a litre of isotonic saline solution or in 5 per cent glucose solution made in distilled water The best veins to choose are the ankle veins The ante cubital veins are useful but as administration has to be continued for sometime the restriction to the patient s movements is considerable If the needle has to be changed because of blocking or other causes the site of injection should be changed

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An 18 gauge transfusion needle is inserted into the vein (arm ankle or back of the hand) and is anchored with adhesive plaster A simple arm or leg splint or bandage is applied to keep the part in position This method is fairly comfortable and avoids 8 separate punctures Local venous irritation however at the site of injection may occur particularly with batches of penicillin which contain impurities If signs of irritation occur the site of injection should be changed at once Heparin (3 units per ccm) has been combined with penicillin in intravenous infusions to prevent thrombosis or irritation but this is not considered advisable If infusion is given at the rate of 35 drops per minute the amount of heparin injected will not materially effect the clotting time of the blood

Technique—The technique of administration is as follows —

To begin with 100 ccm of solution is allowed to un into the vein rapidly after this the flow is so regulated that only 30 to 40 drops per minute are injected In this way it will take one litre of solution from 8 to 10 hours to flow in and then the second litre is given, 100 000 to 500 000 *i u* can be given per day in 2 litres of physiological saline. This is the method of choice in the treatment of severe infections in which bacteraemia is present By this route doses such as 300 000 *i u* to 1 mega units may be given without difficulty Single doses are now not given by the intravenous route unless specifically indi

ons of

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tubing

is said to inactivate penicillin

(5) *Other routes*

(i) *Intrathoracic administration*—In empyema penicillin can be introduced directly into the pleural cavity and if necessary supplemented by systemic ad

ministration Fifty thousand units or more of penicillin may be administered daily by this route the amount being dissolved in 40 to 50 ccm of physiologic saline solution

(ii) *Intra-articular administration*—In suppurative disease of joints 20 000 units or more dissolved in 10 ccm of isotonic saline solution may be instilled into the joint after aspiration As penicillin remains in the joints for longer periods according to some for 24 hours it is not necessary to repeat injections oftener

(iii) *Intrathecal administration*—Penicillin does not diffuse into the cerbrospinal fluid after systemic administration Even 100 000 units by the intra muscular or continuous intravenous infusion do not produce an assayable level of penicillin in the cerebrospinal fluid of patients who have no meningitis but significant amounts are present when meningitis is present In purulent meningitis however effective concentrations can be obtained In neurosyphilis after one or two such large doses as 300 000 to 500,000 units concentrations of about 0 02 unit per ccm were obtained in the cerebro spinal fluid

Ten to twenty thousand units of penicillin can be directly introduced into the spinal canal the whole being dissolved in 10 to 20 ccm of isotonic saline solution Either the sodium or calcium salt may be used Five thousand to 10 000 units may be instilled once or twice daily into the ventricles of the brain if a small tube has been left in place after operation It is however liable to set up irritation (see toxic effects) Sterility of the solution to be injected is of the utmost importance

(iv) *Infusion by bone marrow*—Penicillin can be introduced into the sternum or clavicle or tibia or femur and as much as one litre of solution can be given by this route in 16 hours The technique of injection is the same as for continuous intramuscular drip and the same apparatus may be used This route is used primarily in the treatment where suitable sites are not available for intramuscular injection as in extensive burns and mutilations shock etc and in very small infants.

(v) *Rectal administration*—This route would appear to be unsound because of penicillinase producing bacterial flora Appreciable blood levels of 0 8 units per ccm were however obtained by some workers by a simple oil of theobroma suppository containing 300 000 to 1 000 000 *I U* though the results were irregular others have obtained negative results

(vi) *Oral route*—Owing to rapid inactivation in the acid of gastric juice a large proportion of the penicillin is destroyed when given by mouth Oral therapy is effective in ac[illegible]
simple saline solution pr[illegible]
been adopted by either [illegible]
as near pH 6 as possibl[illegible]
capsules but suspensions in oil were more successful Enteric coating has been tried

Simultaneous administration of a buffer has given satisfactory results and so also a mixture with raw egg Reports with use of sodium or potassium citrate have been favourable but too much alkali also destroys penicillin By using aluminium hydroxide gel magnesium trisilicate or magnesium hydroxide a neutralising action combined with absorption and slow release of penicillin is obtained Tablets of 25 000 or 50 000 units of calcium penicillin buffered

with 0 5 gm sodium citrate have been claimed to give satisfactory results and are available in the market Administration of the sodium or calcium salts 100 000 *units together with 30 ccm of aluminium hydroxide* has been found to give satisfactory results Kolmer (1948) believes that the most satisfactory method of oral administration consists in the administration of tablets of 50 000 units of the calcium or potassium salt the latter being preferred along with 0 5 to 1 gm of sodium benzoate for the reduction of renal excretion and without the addition of a buffering agent

(vii) *Penicillin spray (Aerosol Therapy)* —Systemic therapy by inhalation of a spray is possible and after inhalation of 25 000 units in 25 ccm of physiological saline a concentration of 0 62 units per ccm of blood was obtained for ½ to 3 hours Penicillin can also be given in form of inhalation in such diseases as bronchitis or bronchiectasis the patient inhaling it throughout the day One ccm of physiologic saline solution containing 25 000 units of penicillin can be nebulized or inhaled by a patient in 10 minutes This can be done three times a day and as much as 75 000 to 80 000 units can be administered by this method Penicillin in form of a snuff (5 parts of penicillin by weight 5 parts of menthol and 9 parts of lycopodium) have been used Except in very superficial type of nose infections this method does not give satisfactory results

(viii) *Intra-arterial route*—This route of administration of penicillin has recently been shown to be safe economical and effective in treating severe infections of the extremities A 20 ccm syringe containing 10 ccm of aqueous solution 50 000 units and a No 20 needle is employed For the lower limb the site of election is the femoral artery at the inguinal crease and for the upper *limb the brachial artery at the elbow*

10 Effectiveness Against Infections

Introductory—In the struggle between the tissues of the body and the *infecting organism two things might happen Either there is a complete re*covery or a low grade infection may persist which may produce periodic attacks of ill health later in life If thorough chemotherapeutic treatment is given the infection is often completely eradicated but if it is not there is tendency for the infected individual and the organism to become symbiotic the infection in that case may occasionally lighten up and produce symptoms but otherwise remains dormant The chemotherapeutic effects are mainly dependent upon the size of the dose and the duration of treatment recurrences have been shown to occur in inverse ratio of these two factors In the application of chemotherapy therefore both the size of the dose and the duration of treatment are important considerations

Another important point to be considered is how much damage has been done to the tissues before specific treatment is applied If much tissue damage has occured the result so f [illegible] It is essential therefore that [illegible] is damage has not been done [illegible] ot set in

The action of penicillin and sulphonamides is specific against certain *infective organisms by virtue of their* bactericidal and bacteriostatic action and their power of penetration into the tissues It is important to determine how far the infection has proceeded and how the patient is responding to it The object of application of chemotherapy should be to assist the patient in overcoming

Penicillin therapy—The advantages which penicillin possesses are that it has a powerful action against a group of serious bacterial infections, it is non toxic, it is active in presence of pus and body fluids, and it can be administered in adequate doses to maintain an effective anti bacterial level in the blood and tissues Before giving penicillin it should be determined whether the infecting organism is sensitive to penicillin or not, but this is not necessary if delay is dangerous to the patient The physician may often have to give penicillin after clinical diagnosis only In such cases the clinical course of the disease should be very carefully watched If response is satisfactory it may be felt that a penicillin sensitive organism is being dealt with If, however, after the correct dosage, the clinical response is not satisfactory, the diagnosis is probably incorrect. Within three days of the start of penicillin therapy or even earlier, it should be possible to determine whether the treatment should be continued or not

If the patient is showing satisfactory response to therapy, it has to be determined how long the treatment should be continued In this, guidance has to be obtained from the improvement in the condition of the patient and negative bacterial cultures It may be reiterated here that in chemotherapeutic treatment of infections, early diagnosis and early treatment are of utmost importance

Dosage for systemic therapy—The doses given when supplies were limited were 15,000 units every three hours or 120 000 units in 24 hours by continuous drip method intravenously or intramuscularly This minimum dosage, however allowed little margin for individual variations in patients and the resistance of various strains of bacteria The effective blood level is 0 1 unit per ccm and with 15 000 units every three hours, only a concentration of 0 065 units is reached and with 20,000 units 0 09 units per ccm Consistent results are only achieved with higher dosage and less than 20 000 units (equalling 12 0 mgm or 1/5 gr)

to have overcome the infection In general practice 100 000 to 300 000 units given twice daily produce and maintain the required concentration in blood and tissues Doses as large as half to one million units can be easily given intramuscularly without discomfort Penicillin should be started before bacteria have become established as its effect in primary stages of an infection is much stronger than when the infective process has taken root. If early diagnosis is established a dose of 200 000 units or more up to 500 000 units followed by a second dose of 100 000 to 300 000 units a few hours later have remarkable effects in overcoming the infection.

Acute and Chronic infections—If penicillin is adequately exhibited early clinical evidence of the arrest of an acute infection soon becomes obvious In such cases 100 000 to 300 000 units every 3 to 6 hours produces remarkable effects. It is not necessary to wait for bacteriological reports before starting treatment Chronic infections, however are more resistant and need more intensive and prolonged treatment Surgical measures, if indicated should be implemented without delay as penicillin does not supplant surgery If applied properly and liberally penicillin will prevent abscess and slough formation, but

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The effect of penicillin often is dramatic and is evident in a few hours as shown by fall of temperature disappearance of pain etc In other cases high temperature may persist and only come down at the end of penicillin treatment Fever as such therefore does not indicate failure of penicillin treatment

(1) Infections of blood stream and heart.

(i) *Septicaemia and pyaemia* —The presence of pathogenic bacteria in the blood stream is an indication for immediate intensive and prolonged exhibition of penicillin A proper bacteriological investigation is essential and can give useful indication of progress of treatment but administration of penicillin should be started without waiting for the result The degree of suceptibility of the organism will give a clue to the dosage Bacteraemia or septicaemia were difficult to treat till the discovery of sulphonamide drugs and even with these compounds micro organisms become resistant Further, these drugs are toxic Staphylococcal bacteraemia is not amenable to treatment with sulphonamides but is effectively controlled with penicillin Streptococcal bacteraemia in which sulphonamides have failed has been brought under control as also bacteraemia due to *Diplococcus pneumoniae Neiss intracellularis,* anaerobic streptococci micrococci, micro organisms of the genus proteus and salmonella

Bacteraemia not associated with subacute bacterial endocarditis rapidly yields to penicillin treatment There is no contraindication to the use of penicillin in the treatment of bacteraemia and even very severe cases may recover It is essential however that the concentration of penicillin in the blood be maintained at a constant and effective level during the first few days of treatment Con [illegible] the method of choice and large doses should be given

been demonstrated by frequent bacteriological examinations Treatment should be continued for 4 or 5 days after bacteria have disappeared from the blood and temperature is normal, though injections may be less frequent (300 000 units morning and evening)

(ii) *Subacute bacterial endocarditis* —The great majority of organisms responsible for this hitherto fatal disease are sensitive to penicillin though in varying degrees and with the adequate use of penicillin the infection may be eradicated in as many as 80 to 90 percent of the cases A certain percentage of these however succumb as a result of extensive damage already caused to such vital organs as the heart kidneys etc The earlier the disease is treated the higher the chance of cure In old standing cases and in those who show signs of extensive damage to vital organs the ultimate outlook is not so encouraging

There is no uniformity of opinion with regard to dosage of penicillin and duration of treatment The procedure now generally approved is to give 100 000 units of an aqueous solution intramuscularly every 2 hours for at least 8 weeks after all signs of active infection have subsided Such a dosage schedule continued over such a prolonged period has been found in practice to yield the best results and the smallest relapse rate

Delay in treatment diminishes chances of cure and inadequate doses are naturally prejudicial to success and may give rise to serious complications besides development of resistance in the infecting bacteria Early diagnosis of the disease is therefore, of utmost importance The blood culture usually be

comes negative within a few days after treatment is started, but the fever may persist longer and usually comes down to normal within a week or so If dosage is inadequate, fever returns and relapse occurs

Prophylaxis—In patients suffering from intrinsic cardiac lesions penicillin should be employed as a prophylatic measure before and after surgical procedures such as extraction, of teeth etc which are followed by transient bacteraemia and subsequent subacute endocarditis Administration of 500 000 units daily for not less than 4 days have been suggested

Acute bacterial endocarditis This is a complication of septicaemia The line of treatment is the same as in case of subacute endocarditis, *i e*, at least 10 to 20 mega units daily for not less than 8 weeks Chances of recovery have been greatly improved by such intensive exhibition of penicillin

When sulphonamides are combined with penicillin it is desirable to maintain the concentration of the former drug in the blood at from 14 to 18 mgm per 100 ccm Sulphonamides can be given orally or they can be incorporated in the penicillin solution

Suppurative pericarditis reacts to treatment with penicillin After the pus is aspirated from the pericardium 100 000 units or more of penicillin in 5 to 10 ccm of physiologic saline are injected into the pericardial sac

Infective Phlebitis—If phlebitis is secondary to infection dramatic results are obtained by penicillin therapy The danger of cavernous or lateral sinus thrombosis from a carbuncle of the face mastoiditis or a dental abscess is reduced If this complication arises 100 000 units should be given every three hours intramuscularly, or 0 5 to 1 0 mega unit may be given during 24 hours by intramuscular or intravenous drip

(2) Infections of the central nervous system and special organs.

Sepsis inside the cranial cavity is a serious condition because it raises pressure inside this rigid cavity and because the cerbro spinal fluid has a poor defence against infection Discovery of penicillin and sulphonamides has revolutionized the treatment of sepsis within the skull Many infective processes start from infections in the middle ear and sinuses and on account of improvement in the treatment of these conditions intracranial infection is less frequent Osteomyelitis of the skull (staphylococcal) may occur from infection of sinuses, especially of the frontal sinus Formerly it was practically always fatal Systemic use of penicillin has produced a remarkable decrease in the mortality rate in this condition In the treatment of cranial infections therefore the primary condition should not be neglected

Penicillin unfortunately does not pass the blood brain barrier and it has to be given directly into the cerebro spinal fluid A single dose can however, maintain effective concentration for 24 hours Penicillin if not pure produces irritation but pure penicillin (1 000 *units or more per mgm*) produces *no ill* effects Injections are usually given by lumbar puncture but if the canal is blocked the intracisternal route may be used

Accidental contamination of penicillin with a nonsusceptible organism such as *Ps pyocyanae* may produce death Care must therefore be taken that the syringe, skin etc, are adequately sterilised

(1) *Meningitis* Penicillin is effective against a number of micro-organisms which produce meningitis Meningococcal meningitis produced by *Neiss intracellularis* reacts to treatment with sulphonamides (sulphapyridine, sulphadiazine

and sulphamerazine) and although there has been a considerable reduction, the mortality is still high It should be borne [illegible]
the cerebr[illegible]
evidence [illegible]
in 10 ccm saline should also be injected into the cerebro spinal fluid by lumbar cisternal or ventricular punctures All collections of pus anywhere in the skull should be drained off Fibrinous pus occurs on the surface of the cortex, and for this penicillin is applied locally by means of a flexible catheter passed over the surface of the brain and as it is slowly withdrawn, penicillin 500 units per ccm is distributed over the surface of the cortex

In pneumococcal meningitis good results have been obtained with penicillin Combination of penicillin with sulphonamides gives better results For pneumococcal meningitis, the routine of treatment is the same as with meningo- [illegible]

continued as long penicillin is given, unless toxic reactions occur The course of treatment in this form is longer than in case of meningococcal meningitis

Staphylococcal meningitis is not common and was occasionally cured with sulphonamides Penicillin alone is quite effective in its treatment but it is better to employ sulphadiazine along with penicillin for the synergistic effects

In streptococcal meningitis, penicillin is useful particularly when the hæmolytic streptococcus is present Here again it is advisable to use sulphadiazine in combination with penicillin Cases of recovery in *Str viridans* infections have also been recorded, as also in infection with anerobic streptococcus when sulphonamides and other agents have proved useless Some cases of infection with *H influenzae* have also benefitted

In the treatment of meningitis penicillin should be given early to maintain [illegible] of the cerebro spinal pathways in the cerebro [illegible] of time Penicillin should, therefore be given [illegible] The treatment should be immediately started and should be carried out for seven days or longer if the patient does not recover

(ii) *Wounds of brain and brain abscess*

Penicillin has also been used in cases of brain abscess following trauma to the head and has sometimes been combined with sulphadiazine after surgical drainage has been established The organisms present are usually *Staph aureus* and *str pyogenes* In recent wounds of the brain (up to 72 hours old), calcium penicillin in form of a powder (5 000 units of penicillin combined with one gram of one of the sulphonamides) applied locally is useful In old wounds of the brain, after excision and closure, sodium or calcium penicillin solution (500 to 1 000 units per ccm) are instilled through tubes left in at the operation Pure penicillin given in this way is not irritant Sulphathiazole is not recommended locally in form of a powder as it may cause irritation on direct application

(iii) *Infections of the eye car, nose and throat*

Conjunctivitis—Penicillin has been used in the treatment of conjunctivitis produced by various organisms *e g*, *Staph aureus*, *Str pyogenes*, *Diplococcus pneumoniae* and *Neiss gnorrhoeae* in form of an ointment (30 000 units per gm) and drops (2 500 units per ccm) Drops are put in every hour or even few

minutes as they are easily washed away by the lachrymal secretion Lamellae cause discomfort Pure penicillin is better tolerated than the ordinary form The belief held that penicillin does not diffuse readily into the tissues of the eye is being modified as satisfactory results have been obtained in extensive orbital cellulitis by giving penicillin systemically Subconjunctival injections in doses of 25 000 or 50 000 units in 0 5 ccm of saline give effective concentration in the aqueous and the vitreous humors In purulent conjunctivitis drops put in every few minutes for the first quarter hour and then every half hour for 2 to 3 hours give relief

Keratitis & other conditions—For superficial ulceration conjunctivitis keratitis acute or chronic blepharitis (*Staph aureus*) and dacryocystitis due to sensitive organisms a cream (5 000 units per gram) or a physiological saline solution (1 000 to 5 000 units per ccm) are recommended for local application every one to two hours and continued till there is definite clinical response Crusts in blepharitis may be removed with hydrogen peroxide In severe infections local treatment should be combined with systemic administration of 100 000 units per day Hypopyon ulcer is treated by local application of ointment

Penicillin is of little or no value in the treatment of infections of the central nervous system and the eye produced by *Myco tuberculosis*

In external otitis penicillin is useful as a local application in form of cream or in aqueous drops for a few days Oily drops (1000 to 5000 units per ccm in castor oil) have been used Even infections with *B proteus* which is insensitive to penicillin, have reacted

In acute otitis media in young children two three injections of 50 000 to 100 000 units at intervals of 4 to 6 hours are usually sufficient but treatment is continued for 2 to 3 days For older children and adults 200 000 to 500 000 units are given often with immediate relief If the drum is perforated penicillin powder is blown into the external ear If a solution is used 1 ccm of a solution containing 2000 units or more is instilled into the canal keeping the head tilted and sterile gauze is then plugged in afterwards For less severe cases tablets of buffered penicillin 50 000 to 100 000 units may be given orally every 3 hours day and night

In chronic otitis media mixed infection is often present and penicillin may be combined with sulphonamides Drops containing both substances are instilled into the ear

In mastoditis in acute stages penicillin therapy started early may prevent surgical intervention [illegible]
every 3 or 4 hours anc [illegible]
however be carefully [illegible]
complications

In chronic cases penicillin therapy *may make cortical mastoidectomy possible* instead of the radical operation thus saving the hearing of the affected ear

[illegible]

aqueous spray of ephedrine and this also increases penetration of penicillin and decreases nasal discharge Penicillin spray contains 10 000 units per ccm and if desired this can be combined with ephedrine hydrochloride

Sinusitis In acute suppurative sinusitis local as well as systemic administration of 200 000 to 500 000 units is necessary A single dose may bring relief but it shou'd be repeated after 8 to 12 hours In later stages pus should be evacuated and lavage and instillation of penicillin instituted According to some penicillin has deleterious effect on the cilia of the nasal mucous membrane and they prefer weaker solutions containing 250 units of penicillin per ccm Penicillin therapy is of prophylactic value against spread of infection during surgical interference in nose *e g* removal of polypoid growths etc

Throat—Pharyngitis and laryngitis respond well to local application if the nfecting organism is sensitive In the early stages vigorous local use may abort an attack Sprays are better than use of lozenges In quinsy massive doses *of 200 000 to 500 000 units twice daily prevent* abscess formation Diphtheria bacillus is sensitive and 100 000 to 300 000 twice daily are effective The diphtheria toxin however is not neutralized and anti toxin has to be administered Penicillin has also been used in the treatment of Diphtheria carriers *sometime in combination with sulphathiazole*

In septic sore throat and acute tonsillitis produced by *Str pyogenes* sulphonamides are as a rule successful If these are not well tolerated or are ineffective penicillin gives satisfactory results The preparation used consists of one part by weight of penicillin five parts of menthol and 94 parts of lycopodium the powder is applied six times per day

(3) Infections of respiratory tract

In acute infections of the chest 1 000 000 to 2 000 000 units are usually sufficient spread over a period of 13 14 days Besides this local injections of penicillin into the pleura in doses of 20 000 to 40 000 units repeated every 24 hours may be given if necessary Penicillin is absorbed slowly from the pleura into the blood remaining there for 24 hours If 120 000 to 240 000 units are injected into the pleura sufficient concentration may be maintained in the blood for 48 hours

Pneumonia—For treatment of pneumonia due to *Diplococcus pneumonia,* sulphonamides give satisfactory results They have not been effective in pneumonia produced by staphylococci and streptococci Penicillin should be administered by the intramuscular route or intravenous drip method the former being generally *preferred in doses of 200 000 to 500 000 units twice or thrice* daily, recovery occurs in 2 or 3 days In less acute cases penicillin may be administered in tablet form 100 000 units every three hours day and night Uncomplicated cases do not require more than 3 or 4 days treatment but longer *treatment is necessary in case of pneumonia due to staphylococci streptococci* and susceptible viruses Intramuscular injections are preferred in those cases in which there is marked congestion or if complications are present If bacteraemia due to susceptible organisms is present it is advisable to give penicillin by the *intravenous drip method for the first two days at least In broncho-pneumonia* a mixed infection is often present and a combination with sulphonamides is considered desirable

Briefly though pneumococcal pneumonia responds satisfactorily to sulphonamides penicillin is the drug of choice *It is also indicated (a) when there is no* response to sulphonamides within 24 hours or when there is sensitivity to sulphonamides and toxic symptoms are apparent or there is resistance to these drugs (b) when such complications as leucopoenia liver kidney or heart disease are present

Bronchitis & Bronchiectasis—In bronchitis and bronchiectasis a standard glass nebulizer operated by compressed air is useful Patients can inhale one ccm of nebulized saline containing 2,500 to 5,000 units of penicillin in 10 minutes This should be repeated three times an hour throughout the day and in this way 75 000 to 80 000 units can be inhaled

Penicillin is more useful in the treatment of acute bronchitis than in the chronic form, where probably fibrotic changes have occurred

Emp Lung

In bronchiectasis, where the patient has fever and the organism is sensitive, penicillin is very useful, and should be given simultaneously by inhalation and by intramuscular injections Daily injections of 300 000 units are adequate to supplement aerosal therapy Inhalations of 25 000 to 50 000 units are given three or four times during the day and once or twice during the night It may be beneficial to give streptomycin along with penicillin

Penicillin is useful in the treatment of pneumococcal, staphylococcal and streptococcal empyema, and lung abscess In the former, intra thoracic instillation of penicillin is combined with systemic administration, but often intrapleural administration alone may be successful For intrathoracic administration following thoracentesis, 40,000 to 50 000 units dissolved in 40 to 50 ccm of physiologic saline are injected and left in the pleural cavity, the procedure being repeated once every 24 to 48 hours When surgical drainage has been previously established penicillin is introduced through the drainage tube which is clamped for several hours in order to prevent the penicillin from escaping from the pleural cavity

Treatment of empyema is satisfactory if early diagnosis has been made If, however, pus has been present for days or weeks, penicillin injections should first be given to overcome the infection and then surgical drainage is established if necessary by resection of a rib

In lung abscess the sensitivity of the organism should first be tested Generally, in staphylococcal abscesses, penicillin is useful, and in streptococcal infections results are variable, some are cured others are not If bronchiectasis is also present, results are not good and if multiple infection is present results are variable

Lung abscess—Penicillin 40,000 to 50,000 units is given intramuscularly every three hours If the abscess is drained surgically solutions containing 50,000 units of penicillin are instilled directly into the drainage tube two or three times a day Even in unopened abscess penicillin may be introduced into the cavity, the needle being guided by X-ray

In preparation of patients with suppurative disease of the lung or tumour for surgical operation, penicillin is generally given 4 days to 5 days before the operation as prophylactic

(4) Infections of alimentary tract

Mouth and tongue—In pyorrhoea alveolaris, pockets of pus are formed by deepening of the parodontal sulcus These are not healed by penicillin as they become reinfected after the treatment is stopped In dental surgery penicillin is useful in preventing spread of infection locally and into the blood For this purpose 50 000 to 100,000 units are given quarter of an hour before extraction of septic teeth or other operations A dental cone made from a paste containing penicillin and sulphonamide is inserted into the socket after penicillin in form of lozenges

Pyor

Glossitis—Septic ulcers of the mouth and tongue respond to penicillin treatment and intensive systemic therapy is effective for acute parenchymatous glossitis, vincents angina has been successfully controlled by local use of penicillin in form of lozenges

Acute abdominal conditions—As *E coli* is often concerned *in infections of* the gastro intestinal tract penicillin is generally of little value Penicillin sensitive organisms are however responsible for some infections and the elimination of secondary infecting streptococci of high toxicity by penicillin therapy is beneficial In such conditions as ulcerative colitis however where non susceptible organisms are concerned penicillin therapy is doomed to failure In acute cholecystitis streptococcal infection is common and in early stages intensive penicillin therapy must be employed as curative and later it may supplement operative treatment with advantage In acute appendicitis streptococcal infections may be present or predominant and here penicillin therapy is of value It is particularly useful as adjuvant to operative treatment In peritonitis due to streptococci staphylococci and gonococci massive dosage gives satisfactory results Many strains of *B typhosum* are sensitive to penicillin in vitro but clinical typhoid is not influenced by penicillin though some workers have obtained good results by its combination with sulphathiazole

(5) Bone and joint infections

The crippling effects of bone disease have been almost entirely prevented by penicillin therapy provided early diagnosis is made and treatment is immediately started This prevents abscess formation bone destruction sequestration and metastatic abscesses Penicillin is useful in the treatment of acute osteomyelitis if given before thrombosis of the vessels has occurred Better results are obtained if sequestra are removed by operation and penicillin is given at the same time Spreading osteomyelitis of bones of the skull and face reacts to penicillin treatment If surgically treated it is desirable to combine local therapy with systemic use of penicillin The tendency is to use massive doses in acute haematogenous *infections at the outset a total dose of 400 000 on the* first day 200 000 on the second and 100 000 on subsequent days being favoured At the same time general care of the patient immobilisation prevention of deformity and evacuation of subperiosteal or soft tissue abscess is very important

Chronic osteomyelitis Penicillin is useful in preventing attacks of chronic recurring osteomyelitis which may follow the acute disease If early and adequate amounts of penicillin are given in acute osteomylitis it is possible to eradicate this disease before foci become established Once these are established they are a constant source of trouble In chronic osteomyelitis both systemic and local treatment is desirable along with saucerisation of the focus *immobilisation* and primary closure of the wound

Acute pyogenic-arthritis—In acute suppurative lesions of joints (due to streptococci staphylococci and pneumococci) it is desirable to aspirate 5 to 10 *ccm of the fluid* and instill 50 000 to 100 000 units of penicillin in an equal volume of physiological saline Penicillin should not be repeated till after 48 hours 80 000 to 100 000 units are given by the intramuscular route or intravenous drip It is important that penicillin be given early before irrevocable damage has been done to articular surfaces and structures and this may take place in the course of a few hours If the treatment is started early 2 or 3 injections suffice but it should be continued till conditions become *normal If*

damage has occured to the cartilage, ankylosis will occur In tubercular joints where secondary infection has occured, penicillin is useful in controlling the latter

In hæmarthrosis, aspiration should be followed by direct injection of penicillin into the joint under very rigid aseptic precautions to prevent infection

Prophylactic use of penicillin in connexion with surgical operation of bone has given very satisfactory results, especially in orthopoedic surgery when the patient has a septic focus *Proph*

Compound fractures For prophylactic purposes in compound fractures, it is advisable to give 20 000 units of penicillin
for at least five days in addition to the l
compound powders If infection is already
units every three hours

(6) Infections of the skin

Penicillin is useful where infective organisms are sensitive to it *e g*, *Staph, aureus*, *Str pyogenes*, etc Such common infections are impetigo boils, carbuncles erysipelas, pustular folliculitis, sycosis blepharitis, etc Less common are anthrax and erysipeloids (the bacillus of swine erysipelas) *Ery rhusiopathiae*, *T pallidum* and *Bor vincents* all are *sensitive* Fungi and coliform organism which infect skin are insensitive Local application of penicillin is useful in the majority of cases where infection is superficial but in those cases where it is deep seated as in anthrax, boils carbuncles erysipeloids, etc, penicillin cannot reach the organism it is not effective and it may produce local irritation

Locally, solutions of sodium or calcium salts (500 to 1,000 units per ccm) are applied by means of sprays 2 for 3 times a day This method is more economical than application of creams, but needs a somewhat complicated apparatus A cream containing 27 per cent of arachis oil in water with 13 per cent Lanette wax SX as emulsifier is an excellent preparation If patient is prescribed the cream he is instructed to keep it in a cool place and apply it with a knife which is sterilized by dipping in boiling water before it is put in the cream pot The cream is best applied twice daily *i e*, morning and evening It should be remembered that penicillin cream contains water and retains activity for a shorter period than the ointment If there is no response within a week it is not likely to do good

Penicillin is effective in cases of eczema with secondary infections

Boils & carbuncles—In boils and carbuncles penicillin is quite effective Sometimes, solutions containing penicillin are injected into the deeper layers of tissues around boils and carbuncles This method, however, is seldom necessary as most of the cases respond to systemic use of penicillin in usual doses of 100 000 to 300 000 units twice daily for 2 or 3 days A single dose of 500,000 units may be given to arrest the development of boils Two intra muscular injections of 500 000 units daily, if given early will arrest development of a carbuncle

For injection into the tissues, a saline solution containing 250 to 500 units of penicillin is the best Ointments containing 400 to 500 units of penicillin per gram have been found to be satisfactory for local application

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cocci disappear rapidly Penicillin is also very useful during grafting operations after burns Penicillin therapy may produce sterility of the surface but sometime difficulties arise owing to wound becoming infected with penicillin insensitive organisms It is best to apply penicill n only till the active bacterial invasion is controlled.

Cutaneous syphilis and small pox—Penicillin has been used successfully in the treatment of cutaneous syphilis

Penicillin is useless in small pox but it may be useful in secondary infections complicating the viruses of small pox and chicken pox

(7) Genito urinary infections

E coli plays an important part in infections of the urinary tract and utility of penicillin would appear to be limited It is however of considerable value in infections of the kidney and bladder and tl eir ducts In acute streptococcal nephritis in children 50 000 to 100 000 units 2 or 3 t mes a day are useful In cystitis secondary staphylococcal infections associated with catheters and supra pubic cystostomy are controlled In cases with sudden acute onset a few massive doses should suffice but in chronic cases prolonged treatment is necessary In pyelitis usually there is mixed infection and elim nation of sensitive organisms reduces toxæmia

Perinephric abscess and carbuncle of the kidney have been successfully treated with pen cillin the usual dose given being 100 000 units or more 2 or 3 times a day Single and multiple pyogenic infections of the renal pelvis and urinary bladder have responded well to penicillin treatment

In salpingitis due to sensitive organism massive doses lead to absorption [illegible] umen of the tubes In pelvic cellulitis [illegible] ly started three doses of 100 000 [illegible] hours followed by 50 000 units every

Puerperal Sepsis Breast abscess etc—Provision of an adequate blood level during puerperium and delivery acts as prophylactio in cases of difficult labour where operative procedure is necessary For this purpose 100 000 units or more may be given daily for 2 or 3 days When actual infection has occured an initial dose of 500 000 units followed by adequate doses to maintain a steady level are best. In hospitals the drip method should be employed When septicæmia has occured 100 000 to 200 000 units twice daily give good results

Local application of penicillin in form of cream is effective in the treatment of cracked nipple In breast abscess systemic use combined with local use is best In incipient abscess 100 000 to 200 000 units twice daily for two days often abort abscess formation

(8) Venereal infections

There is no doubt that penicillin is most useful in the treatment of venereal diseases

Gonorrhoea is most easily treated with penicillin Strains of gonococci often become resistant to the action of sulphonamides even when combined with fever therapy and therefore are not eradicated Such patients can be successfully treated with penicillin Striking changes for the better occur in the urethral d scharge within 3 to 4 hours after commencement of penicillin treatment viable gonococci disappearing

In sycosis barbae the infecting organisms are *Staph aureus* and *Str pyogenes* crusts are removed before local application of penicillin infection may not be eradicated in all cases

Cellulitis —In severe cases of spreading cellulitis with bacteraemia good results are obtained with penicill n and erysipelas is also benefitted The skin is infiltrated with 2 per cent procaine solution pus is evacuated by aspiration and penicillin is injected through the same needle 2 000 to 20 000 units being given locally according to the size of the lesion Aspiration and injection of penicillin are repeated every two days It is possible that intensive systemic therapy with penicillin may do away with surgical interference Cellulitis of the fingers and neck is benefitted Recurrent cellulitis of the face though of streptoccocal origin did not improve much after full courses of penicillin for 5 to 7 days Sulphonamides have proved useful in pelvic cellulitis (acute and sub acute) but not in the type due to anaerobic organisms For the acute form a full 7 days course of penicillin is recommended 40 000 units or more every 3 hours If suppuration occurs local injection of 5 000 units of penicillin is indicated

Luawig s angina —Penicillin is effective in the treatment and prevention of severe cellulitis of the neck (Ludwig's angina) and other parts of the body where the infecting organism is usually the hæmolytic streptococcus Penicillin in large doses (1 000 000 units in 72 hours) may be life saving Ludwig s angina is generally due to dental infection in a large number of cases The infection is usually multiple the organisms isolated from these cases being streptococci staphylococci vincent s spirilla micro aerophilic streptococci and gas producing bacteria All these are controlled by penicillin without surgical operation *If a large abscess is present it should of course be opened* and penicillin should be given systemically

Lymphangitis and Lymphadenitis—if due to a septic focus respond well Abscess formation in lymph glands is prevented by early treatment with penicillin

Postoperative parotitis is improved with pen cillin but not epidemic parotitis In the treatment of scarlet fever penicillin has been tried with unsatisfactory results

Infected wounds and ulcers —Local application of penicillin to wounds infected with such gram positive pathogens as clostridia staphylococci streptococci and cornybacteria is useful If gram negative organisms are also present they are not affected and may even increase in number continuation of local and systemic treatment is best in such cases Penicillin is useful in post-operative infection of wounds after all kinds of surgical operations It is also useful in phagedenic ulcers and tropical sloughing phagedena in which fusiform bacilli are present The ulcers clear up with local dressing with penicillin both fusiform bacilli as well as certain spiral organisms are sensitive to penicillin Severe infections of the hand react well to penicillin

Burns —Penicillin has been largely used in the treatment of burns of all

if the surface is large Infecting organisms such as streptococci and staphylo

cocci disappear rapidly Penicillin is also very useful during grafting operations after burns Penicillin therapy may produce sterility of the surface but some time difficulties arise owing to wound becoming infected with penicillin insensitive organisms It is best to apply penicillin only till the active bacterial invasion is controlled

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In salpingitis due to sensitive organism massive doses lead to absorption of the exudate without obliteration of the lumen of the tubes In pelvic cellulitis penicillin therapy should be immediately started three doses of 100 000 to 200 000 units being given in the first 24 hours followed by 50 000 units every 6 to 8 hours for 2 or 3 days

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In the treatment of gonorrhoea in ambulant patients of either sex the method of choice is the administration of a single dose of procaine penicillin 300 000 units Alternatively a total of 100 000 to 150 000 units of crystalline penicillin *in five equal doses at intervals of two hours may be given* Smaller doses are also effective but larger doses are advisable With such treatment the cure rate is more than 98 per cent If prostatitis and epididymitis are present these should also be treated with *penicillin otherwise cure of the infection* may be prevented It should be remembered that about 3 per cent of cases of acute gonorrhoeal infections are likely to be incubating syphilitic infection and there is possibility of symptoms being markedly modified or delayed if penicillin is given This however is not common as most of the combined cases develop the primary sore within 60 days

In gonorrhœa in the female such complications as pelvic inflammation salpingitis gonorrhœal proctitis and vulvo vaginitis yield to penicillin In salpingitis massive doses are given over a period of three or four days In vulvo vaginitis in children 100 000 units or more daily for a few days are effective

Penicillin suspensions in oil and beeswax and procaine penicillin are largely used with excellent results and one single injection of 300 000 units has produced equally good results as 100 000 units in aqueous solution in five equal doses A proportion of failures and relapses occur and many of these respond to a second course Some however require an intensive treatment with increased dosage even up to 1 000 000 units continued perhaps with sulphonamide and fever therapy

Test for cure—*The patient should be watched for at least 12 weeks and* during this period the urine and prostatovesicular secretion should be microscopically and culturally examined A persisting urethritis and cervicitis is very suspicious even when gonococci are not found and the patient should not be declared free until he is symptomless for 3 months

[illegible] —In gonorrhoeal arthritis doses of 100 000 to 200 000 [illegible] *gonorrroeal arthritis complicates gonorrl œal* [illegible] treatment is necessary till clinical improve[illegible]es are obtained Intra articular instillation is not necessary in case of small joints but in case of large joints 50 000 units or more in 10 ccm of normal saline should be injected after aspiration every 24 to 48 hours till three or more injections are given

Gonorrhœal endocarditis is generally a fatal complication as by the time it is recognized infected vegetations have developed Chances of cure have however considerably improved with modern methods of intensive penicillin therapy *i e*, *10 to 12 mega units daily* continued for at least 8 weeks

(9) Syphilis and other spirochætal infections

In the treatment of syphilis the present view is to combine penicillin with [illegible] of penicillin in seven [illegible] ½ gr) of neohalarsane [illegible]re but if these occur [illegible]0 units Relapses are [illegible]jections of arsenoxide [illegible] of bismuth the relapse rate is even lower The efficacy of treatment depends on early commencement the chances of cure decrease with duration of infection and in *late cases much* [illegible] be given An ambulatory treatment suggested by Llyod

Jones and Maitland consists in giving a single injection of 300 000 units daily for thirteen days or 500 000 units daily for ten days in primary syphilis In secondary syphilis 300 000 units are given daily for sixteen days or 500 000 units daily for ten days.

All early cases of syphilis must be observed for at least 2 and preferably 5 years after treatment At least three serological tests should be made during the first 6 months and a further 6 at three monthly intervals for 2 years A full examination of cerebro spinal fluid should be made after 6 and 24 months and skin and mucous membranes examined for signs of muco cutaneous relapse Clinical relapse may occur before the blood tests become positive Sero positive cases may take six months to revert to negative but falling or rising titres are helpful indications

Neuro

After the first few injections of penicillin there may be malaise or headache and primary sore and secondary symptoms may become pronounced General urticaria and in a few cases severe systemic reactions may appear

Syph pregn

In neurosyphilis there is undoubted clinical improvement and penicillin therapy often is combined with malaria therapy or routine chemotherapy A total dosage of 4 800 000 units in seven and a half days is suggested In pregnancy complicating syphilis treatment is started with small doses which [illegible] 1 200 000 [illegible] to 15 days

Herx reac

Reactions resembling that of Herxheimer s occur in more than 50 per cent of cases during the first 24 hours of treatment There may be fever alone or exacerbation of local lesions with or without fever Symptoms are rarely alarming and penicillin can be continued In a few cases skin rash and fever may occur Therapeutic shock (Herxheimer s reaction) may occur in early or late syphilis in case of late syphilis the reaction is severe and may be serious Severe cerebro spinal symptoms may appear in neurosyphilis under penicillin treatment Reduced doses of penicillin given in first 24 or 48 hours may prevent severe reactions

[illegible] worked [illegible] therapy

Other etal d

Penicillin has also been tried in the treatment of yaws relapsing fever and Weil s disease with good results

(10) Miscellaneous Infections

Wounds—If wounds are small superficial and clean dust with penicillin sulphathiazole powder Septic wounds are treated with powder and cream for a day or two before they are sutured For deep wounds pending operation apply cream on sterile gauze If wounds are deep and penetrating penicillin applied locally is not effective

Experience during World War II has shown that in case of ordinary wounds application of powder is effective but in severe and obviously contaminated wounds both local and systemic treatment is necessary 50 000 units being given intramuscularly every three hours or 200 000 units or more by the continuous

method Parenteral treatment is seldom necessary for more than three days and is discontinued generally after 48 hours if the wound is painless and otherwise quiet In severely lacerated and contaminated wounds and those which have been sutured under tension penicillin is continued for 4-5 days and stitches should not be opened for 11 12 days If anærobic infection is present double the amount of penicillin should be given Penicillin therapy with sound surgery is essential for success

Gas Gangrene—Infection with *Cl welchii* is successfully treated with penicillin by local and parenteral application Penicillin however does not counteract the toxins all necrosed muscle and other damaged tissue should be removed and antitoxin should be administered as soon as the presence of the disease is suspected Penicillin should be applied locally in the form of powder of penicillin and sulphathiazole (500 units per gm) or in physiologic saline solution containing at least 1 000 units per ccm it may also be instilled into the wound by means of tubes three or four times a day In addition penicillin should be given in doses of 100 000 to 500 000 units by intramuscular or intraveous drip method till satisfactory improvement is apparent Local or systemic use of penicillin does not prevent development of gas gangrene

Anthrax—Excellent results have been obtained in the treatment of infections with *B anthrax* An initial dose of 500 000 units should be followed by doses of 100 000 units every three or four hours

Actinomycosis—Nearly all strains of *Actinomyces bovis* are fairly sensitive to penicillin Infection of bones such as the maxilla has been successfully treated with penicillin as also abdominal actinomycosis After surgical drainage at least 200 000 to 300 000 units and in some cases more should be given twice daily for three weeks and the course may have to be repeated. After evacuation of pus penicillin solution (1 000 units per ccm) is instilled into the cavity Between the courses a rest period of 2 to 4 weeks should be allowed

Virus Infections—It is known that penicillin is effective in the treatment of ornithosis and psittacosis and such infections in man have been successfully treated with 100 000 units a day continued for 3 to 7 days

(11) Penicillin in veterinary practice

Assays of urine in cows after intramuscular administration 300 000 units of penicillin every 4 hours for five days or till 10 000 000 are given showed that adequate concentrations existed to affect *Cor renale* the causative organism of pyelonephritis Penicillin can therefore be used in bovine nephritis and also other conditions In the milk it only occurs in negligible quantities Penicillin concentration *in the udder depends in part on the extent and rate of absorption* or loss and also on dilution by the secretion of milk Intramammary injection is therefore best

Bovine mastitis produced by *Str agalactiae* which is sensitive to penicillin is easily controlled Mastitis produced by *Staph aureus Str dysgalactiae* and *Str uberis* also react to penicillin but not so well Systemic treatment is not effective and local injections of penicillin in sterile aqueous solution through the teat canal into each quarter of the udder with strict aseptic precautions are useful 20,000 units dissolved in 50 ccm of distilled water are injected into each affected quarter

In horses penicillin is used in the treatment of strangles an acute infection producing inflammation of nasal and pharyngeal mucosa with suppuration of

regional lymphatic glands due to *Str equi* 5 to 9 injections of 100 000 units are given at intervals of 3 to 4 hours Swine erysipelas caused by *Ery rhusiopathiae* is amenable to penicillin therapy

(12) Prophylactic uses

Now that penicillin is available in large quantities it is being used as a prophylactic before surgical and dental operations There is also likelihood of using it on a large scale as an aerosol in operating theatres hospital wards cinemas factories etc

It should also be used as a prophylactic in all potentially infected wounds The minor and more superficial wounds only need dusting with penicillin powder 5 000 to 15 000 units per gm of sulphathiazole sulphamethazine or powdered plaster In civil practice where wounds are attended to quickly 500 units per gm are effective In severe and contaminated wounds both parenteral administration (100 000 to 120 000 units) and local application are necessary In badly infected wounds larger quantities are given the initial dose being 300 000 units

Penicillin was used during the World War II as a prophylactic in case of wounds Most of the dangerous organisms found in war wounds are fortunately penicillin sensitive and here is every prospect of their being inhibited or being destroyed with adequate concentrations of this drug It was applied locally in minor wounds and in major wounds after adequate primary surgery penicillin powder (5 000 units in 1 0 gm of sulphonamide) was applied to the wound Later 100 000 units were given as soon as circumstances permitted followed by injections of 50 000 units at five hour intervals

Penicillin versus sulphonamide – The experience during the World War II showed that penicillin was a more effective agent than sulphonamides in routine prophylaxis in doses of 5 0 gm daily for five days On an analysis of cases treated the number of severe infections was highest when sulphonamides only were given, in the groups which had penicillin only and those who had sulphonamide and penicillin there was no difference showing that sulphonamide did not help The conclusion drawn from these results is that parenteral administration in addition to local use of penicillin is essential in severe war wounds to ensure maximal protection

in form of lozenges or spray
epidemics of diphtheria and
used as a prophylactic agains
producing resistant strains a
with sulphonamides In case of penicillin relative resistance develops b organisms originally sensitive to penicillin have not been shown to have become insensitive

(13) Conditions susceptible and insusceptible to penicillin

The conditions amenable to treatment with penicillin are —

(1) Septic wounds arthritis abscesses carbuncles burns acute and chronic rhinitis sinusitis acute and chronic recurrent tonsillitis acute and chroni pharyngitis quinsy etc —Both local and systemic administration are used

(2) Lobar pneumonia broncho pneumonia acute and chronic recurren bronchitis bronchiectasis pleural effusions and empyemata —local inhalations and systemic therapy

(3) Acute abdominal conditions, *e g*, peritonitis, appendicitis, chlolecystitis etc *chiefly by systemic therapy*

(4) Meningitis otitis media mastoiditis, sinus thrombosis, wounds of brain and its meninges, bone infections, acute and chronic osteomyelitis —Systemic *therapy in large doses and local use*

(5) Genito urinary infections puerperal sepsis, urethritis and arthritis (gonococcal) —Local and systemic therapy

(6) Syphilis in all stages, neurosyphilis, yaws leptospirosis —Systemic therapy in massive doses

(7) Generalised blood infections such as acute and subacute bacterial *endocarditis, streptococcal and staphylococcal septicaemias* —Systemic therapy in massive doses

As prophylactic penicillin is used in all operations major or minor when there is danger of spread of sepsis The tendency now is to give massive doses a single dose of 300 000 units or 100 000 units twice daily The development of oil beeswax combination and procaine penicillin will make it possible for only one or two injections daily to deal effectively with many conditions For local *applications, solutions of penicillin, creams, ointments, sprays drops, snuffs,* powders lozenges, and suppositories, etc , are used

Penicillin therapy should be combined with surgery where collections of pus *septic fluids, etc are present or there are other indications In case of serious* septic conditions *e g*, carbuncles abscesses, etc , a penicillin barrier may be established by injecting round the focus

It should be borne in mind that susceptible bacteria may become resistant to penicillin during treatment It should also be realised that there is no correlation between resistance to penicillin and resistance to sulphonamides Organisms which become resistant to the former are not resistant to latter, the converse is *also true The two drugs can be used together as adjuvants to each other* Every use should be made of these two drugs in the prophylaxis and treatment of infections in a carefully considered manner

The following conditions are considered to be insusceptible to penicillin at present —Typhoid paratyphoid dysenteric infection cholera pneumonia due to Friedlander s bacillus influenza brucellosis, virus infections, pasteurella infections (plague tularaemia), tuberculosis infection with *E coli* organism yeast and *mould infections*

11 Methods of Assay and Standardization

Oxford workers adopted a purely arbitratory unit defined as that amount of penicillin contained in one millilitre of a certain phosphate buffer solution containing ether This is the original O ... s the amount of penicillin which when dissolved i ... inhibition as a certain standard This standard w ... ly arbitrary strength made up in dilute phosphate ... n ice-chest Later it was defined as that amount ... ty millilitres of meat extract just inhibits complete ... aureus' None of these definitions are satisfac ... es relied on their own standards

Provisional British Standard (P B S) This was evolved by the National Institute for Medical Research till establishment of an international unit On this basis *the potency* assigned to it was 155 units per milligram In America a *master standard* was prepared by mixing a number of highly purified crystalline products and this was compared with

The Internat nal Standard was orked o t ly a say ng a large n mber of san ples *Int* B t h and Amer can as con pare l w th U S Master Standard w h ch as p epared from cry a l ne so m ie c l II (G) The t rnat onal u t w uefined as tl e *spec fi a t v ty co ta ed n 0 6 crogra of tl e I t rnat onal P ll Standard* and is appro nmate y eq alc t to tl e Oxford U t Is iu iose to p o de a cl eck on the var ous na onal sta lards a d ho l l ot b s l for rout e as ays The internat onal work n standard cons ts of a sample of calc u n ie c ll w h a po ency of 370 un ts per mgm Th vas d ed and ea ed n tubes conta n ng 6, mgm One nternat onal u t is conta ed 7 m crog ams of the nte at o al s andard un t

br I Va o al Standard as orked out ly taking 30 gm of crystall e sod un pe c ll II d v ded to 30 mgn ealed con a n s Samples of the e c c assayed by s x d ffe e t labo ra or e aga nst tl e e nat onal sta dar l Act v y conta ned n 0 6

wl ch nh b ts the growth of a sens t e st ain of *Stapl aure us* w tl the qua t ty of sta dard tl at produces tl e same nl b t on Deta ls a e g e n the Pharmacopoe a

The U S A Method adop ed by the Food a d Drug Admu strat on s s m lar but is des r bed n more deta l

Dete n n g o ce trat on u body f ds

All me hods for de erm n ng he concei tra on ot pen c l n n va o s body flu ds are ba ed on tests vh cl measu e the deg ee of bacter ostas s produced by the sample under assay

T o metl ods are generaly desc l ed for a ay ( ) by measur ng the d stance hrougl w h cl tl e te t o g s n s nl l ed on an agar p ate bv p n c n sol t o (2) by ob erv ng tl e d lut on of pen c ll n solut on h ch comple ely nh b ts tl e growth of tl e test organ sm n flu d cu ture

Ser al d lu o tl o t—Tl e o ford un t as or gina ly defined as the amo t of *Oxf* pen c ll n h ch when d ssolved n 50 ccm of meat extract b oth vould just nh b t completely the growtl of test stra n of s apl ylococc To le erm e the act v ty of a solut on of unknown strengtl d ut ons of th s and of the standard so t on are made n broth and each s inoculated w th the test stapl hylococ These a e hen ncubated o ern gl t and the d lut on wl ch ompl tely nh b growth s o e l n eacl ca e In mod fica on of se al d lu on ly I amn elkan p a h gh y sens t ve st a n of B hæmolyt c st ep ococcus s used as a test o ga m and red l lood cell as d cator Th me hod s p ol ably nore eas ly adap ed to rout ne cl n cal prac ce The otl er metl od s to note nl b t on of test organ sm on an gar plate ly pen c l n Rap d n etl ds of assay a e nece sa y dur ng manufacture nd for tl s a turb d n etr c me hod us g photo elec r c apparatus l as bee e olved and a curve of tu l l ty s obta ed for bro l ocula ed v th staphyloc cc conta n ng kno vn amounts of pe c ll n W th th the u k o n strength solut on s compared

Me hods have also bee dev ed for assay of creams o nt nents du t ng powders snuffs tablets lozenges o l and bees vax suspens ons

M cro n etl ods—Tl ese are pec ally usef l n assay of blood of the pat ent when h s co d t on just fies the sligl te t nterfere ce It can be carr ed out tl one drop of blood. Other methods such as *Sl de cell Metl od* and *Cap lary tube etl od* ha e been developed.

Cl e cal assay—Th s is based on nact ation of pen c l n by pe c llinase lead ng to the liberation of *pen c llo c ac d wl ch can be directly t trated The method is sa d to g e sa sfactory resu ts*

Color etr c etl od—A coloured compone t is formed by nteract on of pen c ll and N (1 naphthyl 4 azobenzene) ethylenediam ne and a method of color met c de erm na on based on th s react on has been evolved

Est mat t of pe c ll n se s t v ty of infe t g orga sms

Th s is of pract cal n portance n pen c l n the apy These methods al o fall under ser l d lut o me hod or n ea ur ng the d tance to which a c l u e is nh b ted on an agar plate In bo l cases exact measurements a e requ red h control of a standard culture of staphylococci under exactly the same cond t ons

Other methods in use are *Quick assay method of Rake and Jones* in which hæmolysi is used as an indicator, *The Oxford cup method* which is based on the fact that i penicillin is allowed to diffuse into the medium of a plate previously seeded with tes organism a zone of inhibition around the point of diffusion occurs the diameter of thi zone of inhibition is taken as a measure of concentration of penicillin, The *tissue cultur method* in which pneumococcus is used as a test organism and which *grows on the tissu* culture medium

Of the methods devised for determining the presence of penicillin in the body fluid the methods of Flemming and Rammelkamp are commonly used Such methods howeve are not very accurate but give an idea of the penicillin level in the blood and its bacteriostati activity

12. Pharmaceutical Aspects of Penicillin

of

The dispensing of penicillin presents new problems All the aseptic precautions necessar for preparation of an injection have to be taken Contamination with penicillinase produc ing organisms should be avoided The difficulties of sterilization are increased becaus the sterile product has to be prepared from day to day and injections have to be give frequently Moisture has to be excluded pH should be within range of 5 to 8, temperatur cannot be raised, contact with heavy metals (Pb Cu Hg Zn etc) is deleterious as als with alcohol glycerine and oxidising agents

al

Penicillin is included in B P and is defined as the anti infective acid produced by *P notatum* or related organisms grown under appropriate conditions on or in a suitable culture medium converted into sodium or calcium salt The term penicillin is applied to both sodium and calcium salts It is con ... th regard to conditions of manufacture assay stand ... sale etc. It should pass tests of freedom from al ... and tests for sterility etc The sealed containers ... contains the sodium or calcium salt and the total ... The salts are issued in rubber capped vials each containing 100 000 200 000 500 000 or 1 000 000 units of salt One million units equal one mega unit

According to B P penicillin salts must have a potency of not less than 300 units per mgm The samples on the market have a potency varying from 300 to 1,400 units per mgm Pure sodium penicillin can be obtained as white powder *In pure form these salts may* have a potency of as much as 1 666 units per mgm

The reason why penicillin of lower potency is not allowed for parenteral injection is that it gives rise to such *toxic reactions as urticaria and fever* on account of impurities present The B P requires that penicillin for parenteral injections should have a potency of at least 900 units per mgm Preparations with lower unitage are used for making prepara tions for local use *e g*, creams powders lozenges etc

It has already been stated that penicillin has a powerful bactericidal action and its activity is not hindered by the presence of body fluids blood serum pus etc It is excreted in the urine rapidly and for this reason its concentration in the blood falls Repeated doses *have to be given to maintain an effective* concentration in the blood If the solution has to be kept for repeated injections chlorocresol is added as an antiseptic but it is not free from deleterious effects Solutions for intrathecal injection should be free from chlorocresol if the volume for injection is to exceed 15 ccm No aqueous solution should be stored for more than *seven days* even at a temperature of 4°C

Penicillin is rapidly destroyed in presence of moisture Its sodium salt is hygroscopic ... age It is more suited for making aqueous ... r dry preparation such as tablets powders etc. ... not lose their ... The optimum ... ilver mercury ... ensions

Suspensions of dry calcium penicillin in oil or in fatty medium are as stable as the powder, and retain full potency for six months at room temperature. Rancidity in vegetable oils renders it inactive. Penicillin in glucose solutions should not be heated as the pH is likely to fall to 4.0 and it will become inactivated.

Briefly it may be noted that the contact of penicillin with the following is likely to lead to deterioration and should be avoided:

(1) Moisture. (2) The optimal stability is at pH 6 and reaction below 5 and above 8. (3) Temperatures above 10°C. (4) Contact with heavy metals (Cu, Hg, Zn, Sn). Alcohol, Glucose, oxidising agents and penicillinase.

Freedom from bacteria is essential for ointments, creams, etc. to be applied to infected wounds. Although strict asepsis is not necessary for such preparations as ointments to be applied to the skin, lozenges, snuff, etc. sterility is essential to exclude penicillinase producing organisms. Antiseptics if used may produce deterioration. The point of practical importance is that although some of these preparations need not be absolutely sterile they should be prepared under conditions of utmost cleanliness so that they are not grossly contaminated.

In dry conditions (in t…
when stored in sealed tube…
its deterioration and slo…
refrigerators at 4°C. Ph…
in creams, etc. but not u…
than powders but should…
with the degree of purity…

Compatibility.—In dry form penicillin can be mixed with sulphonamides and made into powders, tablets, etc. It is not inactivated by certain antiseptics, *e.g.* chlorocresol 0.1 per cent, chlorobutol, iodized oils, thymol, menthol, etc. It is also compatible with alkaloidal salts such as of ephedrine and adrenaline but not in acid solutions. It is incompatible with R-S-H *group* such as cysteine or thioglycollates, metallic ions, methyl alcohol, ethyl alcohol (except in concentrations below 10 per cent). It is said to be less stable in glycerine than in water.

Administration.—On account of its rapid excretion attempts have been made to combine penicillin with substances which will prolong its stay in the blood by mixing it with benzoic acid or p-aminohippuric acid. Suspensions of calcium salt in arachis oil, beeswax, etc. have been used. Preparations containing calcium penicillin and ethyl oleate have been tried and it was found that though suspension in arachis oil gave a lower concentration in blood it was maintained for a longer period than ethyl oleate.

Aqueous solutions are prepared in a sterile isotonic solution of sodium chloride and occasionally in sterile isotonic solution of glucose (care should be taken to see that it has not turned acid). In the B.P. two solutions have been included for parenteral use, one in normal saline and the other a suspension in oil.

Injectio penicillini B.P. for intramuscular, intravenous and intrathecal use is prepared by dissolving the contents of sealed container (sodium or calcium salt of not less than 900 units per mgm) in pyrogen free physiological saline. When no strength is prescribed one containing 20,000 units per ccm is dispensed. 0.5 per cent chlorocresol is put in as bacteriostatic if several doses are required in the same container but it should not be added to solutions for intrathecal use. Nor should it be added if the volume of doses is more than 15 ccm. No aqueous solution should be stored for more than 7 days at temperature of 40°C. All aseptic precautions should be taken.

In place of *sodium chloride* solution 5 per cent W/V (isotonic) glucose solution may be used, this is said to give a more prolonged action. Solutions containing 5,000 units in 4 ccm of 1 in 50,000 adrenaline are also used for delaying absorption.

Although the B.P. lays down storage for injections at 4°C this is not necessary as storage at room temperature for a week produces no significant deterioration.

Injectio penicillini oleosa (B.P.) for intramuscular use contains 125,000 units per ccm. This preparation is viscous and should be warmed to blood heat before injection but too much heat is undesirable. The syringe to be used is also warmed and both the syringe and needle should be perfectly dry before use. If stored in a cool place this preparation should retain its potency for six months. There is demand for more potent (200,000 to 300,000 units per ccm) suspensions but these are even more viscous than the B.P. injection. For such preparations calcium penicillin of highest potency available should be used. The U.S. Food and Drug Administration recognise three strengths namely 100,000, 200,000 and

Lamellae—These are made with gelatine base each containing 100 to 250 i u

Suppositories—Rate of absorption of penicillin from rectum exceeds the rate of destruction and it is possible to obtain therapeutic concentration in blood by this method Calcium penicillin 0 3 to 1 mega unit oil of theobroma 1 gm (15 gr)

Pessaries—These have a gelatine base and are used for erosion of cervix or infection of vagina

13 Penicillin and Sulphonamides

Penicillin does not appear to be absorbed or destroyed during bacteri inhibition Unlike sulphonamides the action of penicillin is not inhibited in th

affected by tissue lysates in pus, necrotic tissue or blood and it is active in th *presence of large inocula of bacteria* Its disadvantages are that it cannot a present be given by the mouth with certainty of absorption it has to b administered by frequent injections or by drip method it deteriorates in presenc of heat and moisture and it is destroyed in the presence of certain bacteri and enzymes

It is well known that a r

but are not acted upon by

Coli typhoid dysentery grou

bacillus Brucellæ and Pasturellae are acted upon more by sulphonamides but no penicillin and difficulty does not arise as to which should be used

Str viridans haemolytic streptococcus staphylococcus meningococcus gonococcus clostridia (welchii septicum and tetani), *B anthracis* and actinomyces are acted upon both by penicillin and sulphonamides It may be stated in general that in those infections in which bacteraemia suppuration and necrosi are present penicillin should be preferred if these are not present sulphonamide may be used Penicillin is preferable in severe cases of puerperal sepsis cellulitis mastoiditis endocarditis pericarditis peritonitis suppurative arthritis osteomyelitis and badly infected wounds pneumonia (in aged particularly) pneumococcal mastoiditis meningitis and empyema In staphylococcal infection (especially with pus formation) which usually do not readily yield to sulphonamides penicillin should be used In gonorrhœa a routine course of penicillin is preferable and it is also drug of choice in gonococcal arthritis ophthalmia endocarditis pericarditis epydidimitis, prostatitis and peritonitis *Cl œdematis* reacts better to penicillin

...es the action of penicillin

There is however considerable additive effect between penicillin and *streptothricin*

Even sensitive bacteria become resistant to penicillin if they are grown in a culture media containing proportion of penicillin in insufficient quantities to prevent vigorous growth In case of sulphonamides resistance can be readily produced both in vitro and in vivo if an infection is treated with insufficient doses *It has been shown* that penicillin resistance only occurs very rarely in

Briefly it may be stated that the introduction of penicillin has resulted in decline in use of sulphonamides The advantages of penicillin are that it acts in much higher dilutions in the body, its action is not hindered by the presence of pus and tissue lysate products, its margin of safety between the therapeutic [illegible] overtaxed [illegible] nd in some [illegible] resents no [illegible] been considerably eliminated

According to Medical Research Council War Memorandum No 10 (1945) the following indicate the occasions on which sulphonamides should be given and those on which penicillin should be used when available —

Staphylococcal infections —Owing to their poor response to sulphonamide treatment [illegible] the strongest indications for treatment with [illegible] thrombosis severe carbuncle meningitis [illegible] staphylococci from whatever focus, call [illegible] diately Sulphonamides should be tried in [illegible]

Haemolytic streptococcal infections—The vast majority of acute infections due to *Strept pyogenes* respond well to treatment with sulphonamides under present conditions of supply penicillin should not be used unless *adequate* treatment with these drugs has failed. Dolphin and Cruickshank have recently reported encouraging results with penicillin in cases of acute bacterial endocarditis due to haemolytic streptococcus groups A and B which do not respond to sulphonamides (Brit med J 1945 i 807)

Other streptococcal infections—Microaerophilic streptococci such as occur in osteomyelitis (particularly of the facial bones) and in suppurative conditions of the lung [illegible]

Pneumococcal infections—In general pneumococcal infections respond well to sulphonamides and penicillin should not at present be used unless there is good reason for believing the organisms to be sulphonamide resistant Penicillin is nevertheless highly effective in pneumonia, and may be used more when supplies permit In sulphonamide resistant pneumococcal infections particularly meningitis penicillin is strongly indicated

Gas gangrene—All three of the pr[illegible] are more or less equally sensitive t[illegible] varies greatly *Cl oedematiens* being [illegible] considered an unequivocal indication [illegible] disease is not yet proven

Meningococcal meningitis responds so well to sulphonamides that penicillin is rarely called for though it is fully effective In this as in other forms of meningitis penicillin if used, should be given intrathecally whenever possible a short course of intramuscular injections should be given in addition especially in bacteraemic cases

Gonococcal infections—A comparatively small total amount of penicillin administered in a few intramuscular injections during a single day will cure over 90 per cent of cases of uncomplicated gonorrhoea whether acute or chronic and whether sulphonamide resistant or not, and the remainder may be curable by further treatment with penicillin Until recently the general policy has been to treat all cases of gonorrhoea in the first place with sulphonamides and to give penicillin only for sulphonamide resistant infections nevertheless the efficacy and simplicity of penicillin treatment is such that it is rapidly supplanting the sulphonamides for the treatment of this disease

Syphilis—Encouraging results with penicillin have been reported in the treatment of syphilis The sulphonamides have no effect upon this disease

Actinomycosis—Strains of *Actinomyces* infecting man vary in their sensitivity to penicillin The results of treating this infection have nevertheless been generally more strikingly successful than those obtained with sulphonamides

Miscellaneous
anthrax and *dipht*
is yet available bu
La Boccetta & Lock
to anthrax is uncertain Diph
event it should be treated ma
amenable to penicillin the value
results have been claimed Th
effect of penicillin in relapsing
minus or *Streptobacillus moniliformis* and ornithosis (psittacosis) These conditions do not respond to sulphonamides

Local applications—What has been said hitherto about penicillin has referred mainly to systemic treatment *i e* the maintenance by intramuscular or intravenous injection of a concentration of the drug in the blood which is adequate for therapeutic effect Penicillin has also a very wide sphere of usefulness as a local application Its superiority to the sulphonamides for many purposes is due to three causes —

(1) Its efficacy against even larger numbers of bacteria

(2) The fact that nothing in inflamatory exudates antagonises it as breakdown products in pus antagonise the action of most sulphonamides

(3) Its almost complete freedom from tissue toxicity The indications for local treatment with penicillin cannot be detailed here the methods include injection into the sub arachnoid space and into any of the serous sacs and joints instillation into infected areas
is certain skin
uth and throat
sulphonamide
ill n are fully
advantageous

Conditions insusceptible to penicillin—Nearly all gram negative bacilli are resistant to penicillin in greater or less degree (among minor exceptions are *F fusiformis* and the Morax Axenfeld bacillus) these penicillin resistant organisms include the enteric, food poisoning and dysentery groups some but not all strains of *Haemophilus* the genera *Pasteurella* and *Brucella* and several species commonly found in wounds (*Proteus vulgaris Ps pyocyanea* etc)

Myco tuberculosis is completely resistant to penicillin and there is no evidence of therapeutic effect in any virus disease (with the possible exception of ornithosis) or in malaria or any other protozoal infection Rheumatic fever is unaffected as are all forms of chronic arthritis (so far as information goes) except gonococcal Among other conditions for which penicillin like the sulphonamides has been tried without avail are cancer leukaemia and lymphadenoma

STREPTOMYCIN, NEOMYCIN, AUREOMYCIN, CHLOROMYCETIN AND OTHER ANTIBIOTICS

Antibiotics are substances elaborated by micro orgams
antibacterial or antifungal agents It is possible that these sub
as a defence mechanism Pyocyanase was isolated from *Ps*
as 1889 and was suggested in the treatment of diphther
infections Pyocyanin was isolated from *Ps aerogen*
isolated from strains of Actinomyces in 1924 and was
against certain gram positive organisms Citrinin was iso
Ghotoxin from *Tricradrine lignorum* Fumigacin fr
and clavecin from *Aspergillus clavatus* Other s
aspergillic acid, gignatic acid and flavicidin were disc
flavus in 1943 Flavicidin was described in detail i
penicillin in its biologic characters More recently

derived from *Streptomyces aureofaciens* neomycin isolated from a actinomycotic mould and chloromycetin which shows promise in the treatment of typhoid fever All these substances show selective actions against certain micro-organisms Thus far a dozen antibiotics have been described between 1939 1946

Four main groups of antibiotic substances are available (i) antibiotic agents of bacterial origin (spore and non spore formers) (ii) antibiotic agents derived from moulds and fungi and (iii) antibiotic agents derived from Actinomycetes (iv) Antibiotics of non microbial origins

1 Streptomycin

Waksman (1944) announced the discovery of Streptomycin obtained from aerobic cultures of a ray fungus *Streptomyces griseus (Actinomyces griseus)* which he had isolated from the soil about 25 years earlier Streptomycin resembles penicillin in its general properties but shows considerably greater activity against gram negative and acid fast bacilli

Streptomycin is not produced by all strains of *S griseus* and a number of substrains have now been obtained which are more effective producers of Streptomycin than the original culture Meat extract or corn steep liquor are suitable media and the yield is increased with the addition of glucose to the medium Isolation of the drug from cultures is effected by absorption on activated charcoal from which the drug is removed by acidified alcohol This solution is neutralized with sodium hydroxide and ether and after further evaporation under reduced pressure a highly concentrated aqueous solution of the drug is obtained Streptomycin behaves chemically as an organic base in contrast to penicillin which is an acidic substance The hydrochloride and sulphate are the salts commonly used Pure base and pure crystalline salts have been prepared

The original unit of Streptomycin was defined as the quantity of dry substance capable of inhibiting the growth of a given strain of *E coli* in 1 0 ccm of nutrient broth or agar and was called the S unit but the official unit now adopted is the activity contained in 0 001 mgm (1 microgram) of pure streptomycin base (which is equivalent to one original S unit) The potency of crystalline streptomycin base is 1 000 micrograms per mgm and streptomycin issued for parenteral use should contain the equivalent of not less than 300 micrograms of the base per mgm of the dry powder the moisture content of which should not exceed 3 per cent Streptomycin hydrochloride or sulphate now issued in containers containing the equivalent of 1 0 gm (1 000 000 units) streptomycin base

(1) Chemistry

Streptomycin is not a single chemical entity but a mixture of at least two chemically related substances (i) One possessing the structure of an O glyco... of the disaccharide streptobiosamine (N methyl a glucosaminidostreptose) streptidine (1 3-diguanido—2 4 5 6—tetrahydroxycyclohexane) The other is the pure streptomycin B which contains an additional mannose and may be called mannosidostreptomycin Thus chemical structure ...ptomycin has been identified as N methyl l glucosamide streptosido... ...ne Streptomycin compounds such as streptomycin B and dihydro... ...cin and streptomycin calcium chloride complex have recentl... ...and colorimetric and fluorometric methods of ...

Streptomycin is freely soluble in water and in dilute acid solutions but is insoluble in ether or chloroform It is thermostable the powder being stable at room temperatures for 6 to 9 months provided the moisture content is below 3 per cent Solutions are very much less stable and freshly prepared solutions should be used for parenteral administration It is more stable at acid pH level and may consequently survive passage through the stomach It has been shown that though streptomycin is not inactivated by ferments similar to inactivation of penicillin by penicillinase it can be inactivated by certain organic compounds such as cystine, S aminoethanethiol and hydroxylamine It is possible therefore to use cystine to distinguish between the two antibiotics and eliminate streptomycin from certain body fluids

In vitro streptomycin shows considerable antibacterial activity against both gram positive and gram negative organisms In the gram positive group of organisms it is generally less active than penicillin but unlike penicillin it shows considerable activity against the tubercle bacillus In vitro streptomycin possesses considerable antibacterial activity against such pathogenic gram negative bacilli such as *Esch coli, Aerobacter aerogenes, Eber typhosa Shig dysenteriae, Pr vulgaris* as well as organisms such as *H influenzae, Kleb pneumoniae, Ps aeroginosa, Br abortus* and *melitensis, H pertussis Past pestis* and *tularensis* and *v cholerae* As is the case with penicillin, the activity of streptomycin is not considerably affected by the numbers of bacteria present Blood, serum, pus or tissue break down products may how ever increase the tolerance of organisms to the drug by as much as four to eight times

In vivo experiments Feldman and Hinshaw (1944) and later Smith and McCloskey demonstrated the high efficacy of streptomycin in checking and retarding the normal course of experimental tuberculosis in guineapigs Streptomycin was also shown to be very greatly superior to promin and was observed to possess a therapeutic index about ten times better than promin Experimental evidence also demonstrated the value of streptomycin in the treatment The effectiveness of streptomycin in other experimental infections has also been demonstrated Prominent amongst these are *Dipl pneumoniae, Past pneumoniae, Past pestis, Past tularensis Br abortus, Kleb pneumoniae, Borrelia novyi Lept icterohaemorrhagiae,* and *H pertussis* and *influenzae* It also exerts considerable protective effect against spirochaetal infections, though considerably less than penicillin

(2) Absorption, excretion and distribution

Highest concentrations in the blood are obtained immediately following intravenous administration, about an hour after intramuscular administration and still later after subcutaneous injection After oral administration detectable amounts do not appear in the blood stream although high concentrations are found in the fæces Streptomycin is also absorbed after inhalation in the form of spray and aerosols

Streptomycin is excreted mainly by the kidneys but more slowly than penicillin This excretion has been shown to occur mainly by glomerular filtration and is therefore not delayed by drugs such as carinamide which delay tubular excretion of penicillin It is also excreted in small amounts in the bile fæces and sputum

Streptomycin does not diffuse through the tissues as readily as penicillin and low levels are found in the liver and spleen and none in the brain In the blood its concentration is much higher in the plasma than in the blood corpuscles

(3) Modes of administration

The high solubility and low toxicity of streptomycin enable it to be administered parenterally in much the same way as penicillin Thus intravenous administration of 0 5 gm results in immediate high serum levels which fall pro
o rapidly as is penicillin
d and reaches the blood
After oral administra
tine but large quantities
are found in the fæces Small quantities diffuse into the cerebrospinal fluid after systemic administration of a large dose Streptomycin passes readily through the placenta and reaches the fœtal circulation after administration to pregnant women

Streptomycin may be administered by mouth when it is intended that its effect should take place on organisms present in the gut 0 5 gm to several gms may be given per day by this route

(1) *Subcutaneous route* 0 5 gm in 1 to 5 ccm of normal saline or distilled water may be given every 4 hours or at longer intervals There is less local irritation than with penicillin and also less pain than when the intramuscular route is used

(2) *Intramuscular route* In general the intramuscular route is the most satisfactory one and the same technique as for penicillin therapy is advised Due to the slower rate of excretion however it is not necessary to administer the drug more frequently than every 4 hours Recent studies indicate that the frequency of administration can be varied greatly and that when the total daily dose is at least 1 gm results are often comparable whether the drug is given at four six eight twelve or twenty four hour intervals In order to maintain a satisfactory bacteriostatic concentration in the blood it is probably necessary to give the drug every 6 hours Garrod (1948) suggests that in relatively large doses streptomycin is actually bactericidal and that infrequent administration is effective due to the destruction with each dose of a proportion of the bacteria population Recent studies in the therapy of tuberculosis indicate that the entire daily dose of streptomycin can be given in one injection without adverse effect on the therapeutic response

(3) *Intravenous route* Either by continuous drip method or by intermittent injection as much as 4 gm have been given in a day Local irritation occured at the site but was not serious But concentrated solution should not be administered by this route because of the occasional presence of physiologically potent impurities which may produce serious results This route possesses no advantage over the subcutaneous or intramuscular routes and is not commonly used

(4) *Intrathecal administration* 0 1 gm may be given dissolved in 5 to 10 ccm of normal saline or distilled water every 24 to 48 hours

(5) *By spray* Streptomycin can be given satisfactorily by nebulization in the same way as penicillin 0 05 gm being introduced into the nebulizer and inhaled 0 5 gm daily may be given by this method for weeks

(6) *Local administration* Streptomycin may be used locally and may be injected directly in the empyema and abscess cavities Concentrations of the drug of 10 000 100 000 units (10 100 mg) per c c in isotonic solution of sodium chloride have been used

(7) *Topical application* In the treatment of empyema or meningitis concentration of 10 000 100 000 units (10 100 mg) is directly introduced i the pleural cavity or subarachnoid space

(4) Toxic effects

Toxic effects are frequently encountered in streptomycin therapy especia with larger doses and this constitutes one of the chief drawbacks of the dr Minor toxic effects are due to allergic reactions either to the streptomycin to associated impurities Acute histamine like reactions such as *flushing naus* vomiting headache and an abrupt fall of blood pressure may follow intraveno or intramuscular administrations in previously sensitized persons Local irri tion at the site of o impuri and is not influen Irritati of the renal tract occurs or with very high dosage especially where previous kidney damage already exis

Various manifestations of sensitisation reactions characterised by fever a skin eruption of erythematous urticarial maculopapular or even hœmorrhag type (but usually a pruritic erythematous maculopapular type), at first localis are encountered, these are relieved by benadryl Treatment need not be stopp unless it develops into an ex foliative dermatitis Most of the rashes appe from the 3rd to the 10th day of treatment They usually last for only one d but in some cases persist for 7 9 days Contact dermatitis affects hands also face and conjunctiva, sometimes this is so severe as to induce perso affected to wear gloves

The most serious toxic effect encountered with streptomycin when larg doses are given for prolonged periods is complete and permanent loss vestibular function With smaller doses only partial or temporary disfunctio *may result* Deafness *is rare and is met with only in patients treated fo* tuberculous meningitis by intrathecal injections Paraesthesias particularly abou the facial region are common but are usually mild and transitory Psychose may occasionally be met with

It has been noted that even moderate but continuously sustained concentra tions of the drug are more likely to cause toxic manifestations than high pea levels with low levels in between as when the total daily dose is given in one o two injections The newer compound dihydrostreptomycin appears to be les liable to produce neurotoxic symptoms than ordinary streptomycin

Standardisation (i) Microbiological assay—It is usually carried out by th agar diffusion method or the so called cup method in which either a standar strain of *Bacillus subtilis* or *staphylococcus aureus* is used as the test organism The activity of an unknown preparation is determined by comparing the zone *of inhibition produced with that of the standard*

(ii) Test for toxicity in mice—For crude preparation of Streptomycin toxicity was found as follows —LD_0=35 mg and LD_{100}=135 mg per 20 gm mouse by intraperitoneal injection To protect 18 to 20 gm mouse infected with *U Schottmulleri* 6 5 mg of the crude material is usually required For pure streptomycin subcutaneous toxicity in mice is about 1 500 mg/kg

Precautions in using streptomycin One of the most important points that

of stept mycin' on the growth of bacteria Streptomycin at certain concentration levels when injected intraperitoneally in mice infected with *E typhosus* increases rather than decreases the fatality rate

(5) Therapeutic uses of streptomycin

(1) *Extrapulmonary tuberculosis* In generalized miliary tuberculosis where there is no involvement of the meninges streptomycin produces remarkable results and though complete and permanent cure is not attained striking remissions usually result which may last for as long as two years or more A total daily dose of 1 to 2 gm divided into two equal doses should be given intramuscularly morning and evening and should be continued for two to six months according to the response

Meni

In tuberculous meningitis dramatic remissions are often effected by streptomycin though the ultimate fatal outcome is rarely prevented The remissions may persist for many months Streptomycin should be administered by the intrathecal route in addition to intramuscular injections in the dosage given above 0 1 gm dissolved in 5 to 10 ccm of normal saline or distilled water may be given every 24 to 48 hours Intensive parenteral and intrathecal streptomycin therapy is advised a child receiving 200 000 units intrathecally once a day and 100 000 units intramuscularly every 3 hours 27 days after treatment started intrathecal administration is discontinued and the daily intra muscular dose is increased by 100 000 units *i e* total daily dose given is 200 000 units

Perit

Tuberculous peritonitis and enteritis respond very favourably to streptomycin symptomatic improvement being usually manifest within a couple of weeks and complete healing may occur

Tuberculous cutaneous sinuses heal quite rapidly and consistently and recurrences are rare Enlargement of lymphatic glands if present also retrogresses and the infection becomes quiescent Anal fistulæ respond satisfactorily if not of long duration Tuberculous pleural fistulæ often prove refractory to treatment though it has been claimed that healing occurs in more than fifty per cent of cases

Genit tuber

In the treatment of genito urinary tuberculosis although pyelographic studies seldom show any improvement in the renal lesions prolonged symptomatic improvement is usually effected in the great majority of cases Bladder lesions show marked improvement and associated sinuses heal The urine also becomes free of tubercle bacilli in a high per cent of patients In tuberculosis of the kidney the value of streptomycin therapy is chiefly as an adjunct to operation Streptomycin alone may arrest the disease process for a few months but permanent cure can only be expected by excision of the diseased organ

In tuberculosis of the bones and joints streptomycin has proved useful either alone or in combination with surgical measures

Otitis

Tuberculous otitis media responds extremely well to streptomycin and has proved a boon in this hitherto very refractive disease Combined parenteral and topical treatment is suggested in severe cases of tuberculous laryngitis and ulcerating tuberculous lesions of the mucous membrane of the oropharynx In progressive ulcerating tuberculous lesions of the tracheo bronchial tree however, streptomycin will *not benefit fibrous strictures of the tracheo-bronchial* passages

Streptomycin has not proved to be of any value in tuberculous empyema, due presumably to the highly acidic nature of the empyema fluid but the drug is considered to be useful in tuberculous pleural effusion Treatment should not however be prolonged beyond two to three weeks.

(2) *Pulmonary tuberculosis* In general it may be stated that while streptomycin is of unquestionable value in the treatment of selected cases of pulmonary tuberculosis considerable difference of opinion at present exists about the type of lesions where drug should be employed as a routine In practice lesions which are accessible to the blood stream and uncomplicated by irreversible anatomical changes are most benefitted such lesions are mainly exudative early and usually due to bronchogenic or hæmatogenic dissemination Because of the regularity with which streptomycin produces resistant strains of the tubercle bacillus its use is not advisable in such cases as would have a good prognosis without chemotherapy Chronic fibroid and fibrocaseous tuberculous lesions are also not suitable for streptomycin therapy Ulcerating lesions of the bronchi and trachea are very favourably influenced as also is tuberculous laryngitis and ulcerating lesions of the mouth and pharynx

Perhaps the greatest value of streptomycin in pulmonary tuberculosis is that it makes surgical treatment feasible in such cases where this would otherwise not be possible Thus in fibrocaseous and fibrocavernous disease strepto-

and reasonably safe Pneumothorax can often be established more expeditiously and safely in acute pneumonic tuberculosis after a course of streptomycin

Administration dosage and toxic effects In earlier days streptomycin was administered to tubercular patients in doses ranging from 1 to 3 gms a day for two to six months and toxic reactions especially damage to the vestibular apparatus were frequently encountered Recent investigations however have demonstrated that streptomycin in daily dosages of 0 5 to 1 gm apparently yields as good results as were obtained with the higher doses employed previously It has also been shown that when the total daily dose is at least 1 gm the therapeutic response is as good whether the drug is given at intervals of 4 6 8 12 or 24 hours Thus it appears likely that the total daily dose can be given in one single daily intramuscular injection. With this reduced dosage and increased interval of administration the incidence of toxic reactions is also greatly decreased

Bacterial resistance in tuberculosis One of the chief disadvantages of streptomycin therapy in tuberculosis is the ease and rapidity with which highly resistant strains of *Myc tuberculosis* develop In a recent study *Pyle (1947)* found that in approximately 75 per cent of cases investigated the bacterial population became predominantly resistant after six to sixteen weeks of treatment and bacilli resistant to such high concentrations as 3 000 micrograms of streptomycin per ccm of medium have been recovered from patients It is because of this development of bacterial resistance that the concensus of opinion at present is that in most cases the administration of streptomycin should be limited to five or six weeks or even less In relapses treatment can be resumed if the organisms are still sensitive to streptomycin in vitro

Contra indication of streptomycin therapy in tuberculosis —

(1) Chronic fibroid or fibrocaseous pulmonary tuberculosis

( ) [illegible] and apparently terminal type of tuberculosis

(iii) Minimal or early moderately advanced pulmonary tuberculosis with favourable prognosis

(iv) Chronic empyema of tuberculous origin

(v) Streptomycin treatment should be avoided when other treatments are available, because to produce a drug resistant strain of tubercle bacilli by such treatment may possibly make any other form of treatment ineffective, should a more serious type of tuberculosis subsequently develop.

(3) *Brucellosis* Spink et al (1948) consider a combination of sulphadiazine and streptomycin an effective form of therapy for human brucellosis They advise a dosage of streptomycin 2 gm per day (0 5 gm every 6 hours intramuscularly) for 7 to 12 days together with sulphadiazine 4 gm initially and 1 gm every 4 hours thereafter, for 2 to 3 weeks Hielman (1949) in a study on mice infected with brucella organisms showed that streptomycin or dihydrostreptomycin in combination with aureomycin was most effective Herrel and Barber (1949) obtained very good results in a small series using dihydrostreptomycin 2 gm a day in divided doses intramuscularly combined with aureomycin 3 gm a day by mouth in divided doses every 6 hours All patients promptly recovered without recurrence.

(4) *Tularaemia* Streptomycin yields very good results and for adults 2 gm daily in divided doses is continued for 5 to 8 days For children and adults below 50 kg in weight the total daily dosage should be 0 04 gm per kilo body weight The drug should be stopped if deafness vertigo etc appear

(5) *Hæmophilus influenzæ pneumonia* A combination of streptomycin and sulphadiazine gives good results The usual dosage of sulphadiazine is combined with 2 to 3 gm per day divided into six 4 hourly doses intramuscularly

(6) *Klebsiella* (Friedländer) *pneumonia* Sulphadiazine is given together with streptomycin 0 5 gm every 4 hours (3 gm per day) till the sensitivity of the infecting organism can be determined after which the dose may be increased if necessary, so as to maintain a blood concentration at 4 to 8 times this level The treatment is continued for three days after the temperature falls to normal Streptomycin is employed in the same way for lung abscess due to Friedländer and colon bacillus organisms

(7) *Granuloma Inguinale* Streptomycin has proved to be the most valuable drug so far for this condition A dosage of 4 gm per day is given in divided doses every 4 hours for 5 days, but with this high dosage a careful watch must be kept for toxic effects Recurrences may respond to a second course of streptomycin

(8) *Subacute bacterial endocarditis* Where the causative organisms are resistant to penicillin, *e g* infections with *Esch coli Aerobacter aerogenes Hemophilus influenzae, Klebsiella pneumonia Brucella Past pestis Pseudomonas aeruginosa, etc*, streptomycin is given in doses of 2 to 5 gm daily in divided doses for six to eight weeks

(9) *Acute appendicitis* For perforated appendix streptomycin 2 gm a day in divided doses is given for 3 to 5 days postoperatively in combination with penicillin 400 000 to 800 000 units a day In the conservative treatment of appendix abscess give streptomycin 1 5 to 2 gm a day in addition to penicillin

400 000 units per day The patient must be carefully watched for signs of spread of infection or rupture when of course recourse must be had to immediate operative interference

(10) *Bronchiectasis* Antibiotics are of value in controlling associated acute superimposed respiratory infection and in preparing patients for pulmonary resection or thoracoplasty Penicillin and streptomycin either alone or in combination may be used Streptomycin 0 5 gm dissolved in 20 ccm of normal saline should be nebulized in 3 or 4 sessions every 24 hours In addition 0 5 gm of streptomycin is given daily by intramuscular injection

(11) *Chronic ulcerative colitis* In the acute and subacute toxic phases streptomycin 0 5 gm 4 times a day should be started immediately together with sulphadiazine 1 gm orally 4 times a day Both the drugs should be continued for two weeks

(12) *Agranulocytosis* The causative drug should be stopped immediately and penicillin 40 000 units given every 3 hours till the neutrophils return to the circulation in normal numbers If the infecting organisms are sensitive to it streptomycin 0 25 to 0 5 gm may be given in addition every three hours

(13) *Plague* A large number of recent reports have confirmed the value of streptom
2 to 3
sulphat
least three days after the fall of temperature to normal Suppurating buboes are dealt with surgically as necessary

(14) of
septic abort a
satisfactory n
1 gm daily may be given in 3 or 4 divided doses

In acute cholecystitis with perforation or impending perforation in preparing the patient for operation streptomycin 0 5 gm intramuscularly every 4 hours may be given instead of penicillin or if the organisms cultured from the peritoneal cavity are penicillin resistant

In the initial conservative treatment of acute pancreatitis streptomycin 0 5 gm every 4 hours may be given instead of penicillin

In acute mastoiditis if there is failure to improve with penicillin or sulphadiazine and the infecting organism is streptomycin sensitive give streptomycin 0 3 gm every 3 hours day and night for adults and 0 02 gm per kilo body weight daily for children below 40 kg Development of deafness or vertigo are indications for stopping the drug

For chronic otitis media wicks moistened with streptomycin 2 500 units per ccm are effective in infections due to *B pyocyaneus* Treatment should not be continued beyond ten days due to the risk of development of skin sensitivity

In the treatment of acute regional ileitis it has been reported that approximately 25 per cent of cases resolve with the combined oral and parenteral use of streptomycin The drug should be given in doses of 1 gm a day by mouth combined with 0 5 gm 4 times a day by intramuscular injections

In the post operative treatment of cerebral abscess if the organism is not sensitive to penicillin streptomycin should be given in doses of 0 25 gm every 3 hours for two weeks

In preparing patients for the surgical treatment of intestinal tumours streptomycin should be given orally 0 5 gm every 6 hours for 48 hours before the operation till the temperature has been normal for 24 hours

In pyogenic liver abscess streptomycin 0 25 gm every 3 hours may be given in addition to penicillin 100 000 units every 3 hours If with this regimen the fever does not subside in 2 or 3 days immediate operative interference is called for

2 NEOMYCIN

Streptomycin has two serious disadvantages in the therapy of tuberculosis its toxic effects on the central nervous system particularly in the 8th cranial nerve and the ease with which it produces resistant strains of the tubercle bacillus After examination of thousands of cultures of actinomycetes from the soil belonging to the genus *Streptomyces fradiae* (*Actinomyces fradii*) Neomycin is isolated by Selman A Waksman from cultures by methods of absorption and elution similar to those employed for streptomycin It is a basic water soluble compound and most active at an alkaline solutions which is stable to heat and is active against a wide range of gram negative and gram positive organisms especially mycobacteria but not against fungi It is insoluble in organic solvents In vitro tests show it to be equally active and in some cases even more active against streptomycin sensitive and streptomycin resistant strains of tubercle bacilli Studies thus far have demonstrated its low toxicity and lack of tendency to produce resistant strains

Stabi

The following is a list of organisms susceptible to the action of neomycin experimented upon so far —

Escherichi coli Bacillus subtilis B mycoides, Staphylococcus aureus Mycobacterium 607, M ranae M avium M phley B cereus S lutea Ps aeruginosa Pr vulgaris Bodenheimer's organism Serratia marcescens Mycobacterium 607Rs Trichophyton mentagrophytes Candida albicans

Acti

Neomycin preparations are found to possess several desirable properties — (a) similar activity against both streptomycin sensitive and streptomycin resistant bacteria (b) considerable activity (in some cases greater activity than streptomycin) against various forms of *M tuberculosis* and other mycobacteria (c) limited toxicity to animals or none, (d) activity against various bacteria *in vivo* including gram positive organisms and against both streptomycin sensitive and streptomycin resistant organisms (e) lack of resistance against neomycin among the organisms sensitive to it or only limited development of such resistance

Since neomycin has not yet been obtained in crystalline form very little can be said of its chemical nature Preliminary results however point to its being distinctly different chemically from streptothricin and form streptomycin

3 AUREOMYCIN

Aureomycin is an antibiotic derived from a strain of *Streptomyces aureofaciens* It was discovered by B M Duggar while working at the Lederle Laboratories Division of the American Cyanamid Company The antl ...

Iv Rickettsiae and certain viruses

(1) *Chemistry* —Aureomycin is a weakly basic compound which contains both nitrogen and nonionic chlorine Aureomycin when treated with alcoholic ferric chloride gives a greenish brown colour by reflected light and reddish colour by transmitted light The crystalline free base has the following properties m p 168 169°C (uncorr) Solubility in water 0 5-0 6 mgm per ml at 25 0°C very soluble in the cellosolves dioxane and carbitol Very soluble in aqueous solution above pH 8 5 Somewhat less soluble in isotonic sodium chloride solution These solutions are acid (pH 4 5) Aureomycin is soluble in acid and alkaline solution but is almost insoluble at pH 7 It is available as a yellow crystalline hydrochloride salt

The activity of this antibiotic deteriorates rapidly in alkaline solutions at room temperature At pH 2 5 the substance is stable but at pH 8 5 25°C it loses its activity Aureomycin kept in dry powder form in sealed ampoules or in capsules retains its potency for at least seven months at room temperature Solutions kept frozen at 20°C retain their activity for long periods

After oral administration aureomycin is rapidly absorbed through gastro intestinal tract The oral route of administration is preferred because the drug is promptly absorbed and the results are uniformly consistent

A qualitative assay is difficult but quite low levels like 0 3 2 5 mg per c c have been detected in the blood serum The plasma levels after oral doses of upto 1 gm given six hourly have usually been found to be about 2 micrograms per millilitre or less but the methods of estimation however were not satisfactory Harnod and co workers (1949) found that in therapeutic dosage in dogs aureomycin readily passes the blood brain barrier and substantial amounts remained in the blood stream (4 0 micro grams per c c) and in the cerebrospinal fluid (0 8 micro grams per c c) two hours after an intravenous injection Schoenbach and co workers (1949) found 1 2 to 2 4 micrograms per c c in the serum following an intramuscular injection of 40 mgm in patients who had been *on therapy for 5 to 14 days Wright and co workers (1948) found* that the highest blood levels occured two hours after oral administration of 300 mgm 2 micrograms per c c of aureomycin

Aureomycin is very rapidly excreted in the urine and the excretion continues for 2 3 days after a single dose of 0 5 0 75 g Levels upto 320 gm per c c have been detected after oral administration The greatest rate of *excretion in the urine occurs between 4 8 hours after* oral administration The rate of excretion remained relatively constant for at least 6 hours while after intravenous injection the excretion was rapid during the first two hours slower between the second and fourth hours and low between the fourth and sixth hours

(2) *Toxicity* —The acute toxicity of aureomycin was determined in mice rats rabbits and dogs The oral toxicity was found to be low the mortality in mice being only 5 per cent at a dosage of 2 500 mg per kilo The LD_{50} on intravenous injection in mice is between 50 and 100 mgm per kilogram of body weight The LD_{50} on subcutaneous injection in mice is between 3 000 and
ight Rapid intravenous injection of 150 mgm
illed a dog and produced haemoglobinuria
per l_{b} of body weight) of aureomycin were
oderate local reaction and some loss of weight
associated with anorexia Autopsy revealed no gross or microscopic abnormality

Toxic manifestations in human beings—Toxic effects were minimal and infrequent except after intravenous administration. As a whole the drug is well tolerated and is relatively non toxic for all practical purposes when given in therapeutic doses. The commonest complaint during large doses of aureomycin are looseness of the bowels with frequent and bulky stools but true diarrhoea is uncommon. Nausea and occasionally vomiting occurred after one or more doses in a few patients. Anaemia attributable to the drug did not occur and no depression of the cells in the granulocytic series is observed. There is no evidence of renal irritation, fever or rashes during the period of aureomycin therapy. In a few cases of cystitis a disagreeable drawing or squirming sensation was noted in the pelvis which may be related to the high urinary acidity. No neurological abnormalities like nystagmus, vertigo, tinnitus or auditory disturbances have been observed. An intramuscular injection leads to local irritation and variable degrees of pain from moderate to severe and lasting from several minutes to several hours. Patients and normal individuals ranging in age from 34 to 45 years have been given from 15 to 30 mgm per kg of aureomycin daily over a period of 5 to 20 days. Braley and Sanders (1948) stated that while aureomycin is moderately irritating when injected intramuscularly the addition of a small amount of procaine hydrochloride almost completely prevented discomfort. Topical administration of aureomycin in patients with staphylococcal ophthalmic infections indicated that an ointment containing the hydrochloride was irritating to nearly all patients although active against the infection while an ointment prepared with the Borate was non irritating but probably quickly lost its activity.

(3) *Factors Influencing Aureomycin Activity.*—Aureomycin is effective only against vigorously multiplying organisms but not against fully grown or resting cultures. Aureomycin is much more effective in an acid than in an alkaline medium, the reverse of streptomycin. Filtration of solutions of aureomycin in water, broth or urine through Seitz, Mandler or sintered glass filters does not appreciably reduce the activity of aureomycin.

There is no significant tendency for the development of resistance to aureomycin in organisms either *in vitro* or *in vivo*. This is in sharp contrast to streptomycin. All organisms of the same species isolated from the same patient before, during or after the treatment with aureomycin for varying periods upto one month or longer were equally sensitive to this antibiotic.

(4) *Action on Micro organisms.*—Aureomycin possesses bacteriostatic and bactericidal activity against numerous gram positive and gram negative bacteria. Its activity deteriorates rapidly in alkaline solution. Human serum also decreases its activity. The following organisms are susceptible to aureomycin:—

(1) *B haemolytic streptococcic* strains Group A, D, F and G
(2) *Diplococcus pneumoniae* Types I, II and III
(3) Staphylococci
(4) Some strains of *B coli aerogenes*
(5) *Klebsiella pneumonia*
(6) *H influenzae*
(7) *Brucella suis and abortus*

Pseudomonas aeruginosa and strains of Proteus are not inhibited even in high concentrations.

(5) *Indications for use.*—Aureomycin hydrochloride (Lederle) is a yellow crystalline antibiotic potent against many gram negative and gram positive organisms as well as highly specific against Rickettsial infections. It is also

effective against primary atypical pneumonia, an infection of unknown etiology. Aureomycin should be used against infections that have become resistant to penicillin, streptomycin, or sulfonamides and in patients who exhibit severe and uncontrollable sensitivity to these drugs. The following are the diseases acted upon successfully by aureomycin :—

(a) Rocky mountain spotted fever.—This disease is caused by *Rickettsia rickettsii*, the vector being the common tick. Aureomycin appears to be specific for this organism. Wong and Cox (1949) found that this drug possesses marked effectiveness against the rickettsiae of spotted fever, typhus fever, scrub typhus fever and Q fever in chick embryos. The drug is given orally initially in doses of 0.5 gm. every 6 hours followed by slightly higher doses for 4 days. Temperature responds in about 3 days, the only side effects during the administration of the drug is large loose motions found in very few of the patients.

(b) Q fever.—This is an acute infectious disease of rickettsial type caused by *C. burnetii* and prevalent particularly on the west coast of the United States and Canada. Aureomycin is given in oral daily dosage varied from 2 to 5 grams. Cases running a febrile course for many days before treatment required a correspondingly longer period of treatment, whereas cases that had been febrile for only a few days required a correspondingly brief period to restore the temperature to normal.

(c) Rickettsial pox.—This relatively new disease, an outbreak of which has recently occured in New York City, appears to be controlled by aureomycin.

(d) Exanthematous typhus.—An average daily dose of 200 mgm. per kg. of body weight are given orally over a period of 36 hours (the total dose being 300 mgm. per kg. of body weight). The results are excellent. Within the first few hours of treatment headache and muscle pain usually disappear and in 36 hours temperature usually comes down to normal.

(e) Recrudescent epidemic typhus (Brill's disease).—The initial dose was 200 mgm. orally every hour for 3 doses and thereafter every 2 hours day and night.

(f) Primary atypical (virus) pneumonia.—1.5 gm. orally as initial dose is given followed by 1 gm. every 6 hours and continued for several days after the temperature has become normal.

(g) Pyaemia and osteomyelitis.

(h) Pyoderma gangrenosum in chronic non specific ulcerative colitis.

(i) Virus diseases like lymyhogranuloma venereum and psittacosis ("Parrot fever").—Aureomycin appears to improve markedly acute ulcerative and inguinal forms of lymphogranuloma venereum. Chronic cases with advanced perirectal and similar changes require various adjuvant measures, including surgery. Aureomycin was stated to be the treatment of choice in all cases of lymphogranuloma venereum infections—together with surgery whereever mechanical conditions demand it. Wong and Cox (1949) have shown in experimental animal that aureomycin possesses marked therapeutic activity against the entire group of psittacosis—lymphogranuloma viruses.

(j) Bacterial infections (including many gram positive and negative organisms, acute and chronic Brucellosis due to *Brucella melitensis*, Tularaemia sulphonamide penicillin streptomycin resistant organisms, Coli aerogenes group of infections of the urinary tract and peritoneum).

(k) Ocular infections (bacterial and viral).

(i) Bacterial infections —Braley and Sander (1948) have recently reported that aureomycin borate is effective in 0 5 per cent concentration in staphylococcic, pneumococcic and influenzal conjunctivitis It is also effective in infections caused by the diplobacillus of Morax Axenfeld and Friedlander s bacillus

(ii) Virus like infections —Several eye infections that are thought to be viral like in nature respond to aureomycin including conjunctivitis follicular conjunctivitis and herpes simplex corneae (dendritic keratitis)

Ophthalmic infection may usually be controlled by the use locally of an ophthalmic solution made by adding 5 c c of distilled water only to 20 mgm of aureomycin contained in a dropper bottle designed for this purpose by Lederle If this solution be kept under refriegerator conditions it will remain stable for approximately two days Combined local and oral therapy is preferred in Diplobacillus (Morax Axenfield) ulcers Friedlander bacillus ulcers and in general where there is severe infection One or two drops should be placed in affected eye or preferably in both eyes every two hours or oftener depending upon the severity of the infection Aureomycin hydrochloride ophthalmic solutions should be made up fresh every two days

Op inf

(l) *Gonorrhœa* —*If the gonococcus become resistant to penicillin* aureomycin may be used In order to equal the effect produced by a single injection of 300 000 units of repository penicillin the total dose of aureomycin should be greater than 1 5 gm and be given over a period of 2 days Chen and co workers have called the attention of the medical profession to the fact that aureomycin is the first chemotherapeutic agent to have been reported effective against all 5 venereal diseases namely lymphogranuloma venereum gonorrhœa granuloma inguinale chancroid and syphilis

(m) Meningococcus —Collins and co workers have reported a case of meningococcemia in which aureomycin was begun 12 hours after the onset of symptoms The dosage employed was 500 mg for 4 doses 350 mgm for 4 doses and 250 mgm for 3 doses at 6 hour interval

(n) Escherichia coli —Fine Seligman and Frank have stated that aureomycin is the most effective drug now available for E coli peritonitis

(o) Bacteroids Funduliformis septicaemia —Sprout and co workers have successfully treated cases of *Bacteroids Funduliformis* septicaemia with aureomycin

(p) Infections caused by hæmophilus organisms —*Hæmophilus pertusis*— At present aureomycin is the most promising agent for the control of this infection 0 5 gm of aureomycin per kilo being given in devided doses over a period of 4 to 8 days

Hæmophilus influenza —It is equally effective against *Hæmophilus influenza*

(q) Syphilis —Relief of cutaneous syphilides and of complicating fusospirillary infections have been obtained but the serology seem to have been unaffected Prompt healing of the primary and secondary lesions usually took place with a marked quantitative changes in the Kahn reactions

Aureomycin has been found useful against the following organisms but its full therapeutic value has not yet been determined —

(a) Salmonella organisms (the drug is effective in large doses)

(b) C

hours Smadel Woodward et al (1948) in a report on 25 cases of scrub typhus caused by *R tsutsugamushi* in Malaya showed that chloromycetin therapy resulted in rapid and complete recovery in all the patients so treated The dosage recommended is 60 mgm per kilo initially followed by 0 25 gm every 3 hours *for seven doses or until the temperature falls to normal*

(b) Scrub Typhus—In the army in Kashmir, cases of scrub typhus rapidly yielded to a total dosage of 3 gm of chloromycetin *An initial dosage of 60 mgm* per kg of body weight is recommended followed by 0 25 gm every 3 hours for 7 doses or until the temperature has become normal

(c) Rocky Mountain Spotted fever—Dramatic evidence on the beneficial effect of chloromycetin therapy was obtained in a series of cases of Rocky *Mountain Spotted fever The temperature fell to normal within 76 hours and* other symptoms such as headache and mental confusion started improving on the second day of therapy The initial dose of 60 mgm per kilo body weight *should be followed by 0 25 gm every 3 hours till the temperature has been* normal for 48 hours

(d) Typhoid fever—In typhoid fever chloromycetin has yielded the most satisfactory results The temperature begins to fall within 24 to 48 hours and returns to normal in 3 to 4 days Symptoms begin to improve even more rapidly and patients generally feel comfortable after 24 hours resolution is obvious after 48 hours An initial dose of 50 mgm per kilo body weight is followed by 0 25 gm every 2 hours until the temperature has returned to normal after which 0 25 gm may be given every 3 or 4 hours for another five days Blood culture in some cases become negative within 4 days of treatment In some of the cases reported on clinical trials the average total dose of chloromycetin used is between 18 to 24 gm Toxic symptoms are noted in nearly half of the cases and included nausea vomiting distension diarrhœa retention *of urine delirium convulsions rash and stomatitis*

(e) Undulant fever—Patients with active undulant fever have been favourably influenced by chloromycetin therapy although the response is not so good in the chronic diseases The usual initial dose of 60 mgm per kilo body weight is followed by 0 25 gm every 3 hours for at least 7 days of normal *temperature*

(f) Primary atypical (virus) Pneumonia—Chloromycetin has been used with success in a limited number of cases of primary atypical (virus) pneumonia The dosage employed has been 0 5 gm every 2 to 3 hours for the first 6 doses and then 0 5 gm 4 times daily The temperature may fall to normal within 36 to 48 hours and it is advisable to continue the drug for another 3 to 5 days to prevent relapse

(g) Bacillary urinary infections—*In vitro* the drug has favourable effect on the colon group of organisms *In vivo*, with an oral dosage of 2 to 3 gm daily divided into 2 to 4 parts daily the urine has been found to be free from bacteria in 1 to 3 days The drug should be continued in dosage of 0 25 gm 3 to 4 times daily for 5 to 7 days after the urine has become free from bacteria

In bacillary infections of the urinary tract infections with *E coli Aerobacter aerogenes Pseudomonas aeruginosa Klebsiella Pneumonia Salmonella schottmuleri* and *B proteus* have been found to respond favourably to chloromycetin The same initial dosage as above is employed after which 0 25 gm 3 or 4 times a day should be continued for 5 to 7 days after the urine is

Polymyxin

It is an antibiotic substance in the metabolic products of *Bacillus polymyxa*, n organism which is relatively common in soil The name is given as Aerosporin by the Wellcome Physiological Research Laboratories and Polymyxin by the research workers of the American Cyanamid Company Well come research workers later named their original product as Polymyxin A instead of 'Aerosporin', while the American Cyanamid product is distinguished as Polymyxin D All the substances are similar in showing high activity against gram negative organisms, including *Haemophilus pertusis* and *Klebsiella pneumonia*

In vivo experiments on mice with *Eberthela typhosus* or *K pneumonia Aer* showed that Polymyxin D has about 1/10th the activity of the A form but the toxicity of A form was found to be about 3 times that of D form The main difference in chemistry between the two forms is that D contains the amino acid series All antibiotics of the series appear to be basic polypeptides some or all of which contain L a y diaminobutyric acid pleucine L threonine and a fatty acid of the empirical formula $C_9 H_{18} O_2$ At John Hopkins Medical School Polymyxin D was found to be more toxic than Streptomycin in experi mental animals on a weight basis, on the other hand it was also considerably more effective against *K pneumonia* Against gram positive pneumococcus type 1 in mice it was relatively ineffective The toxic action was found to be exerted mainly on the tubular epithelium of the kidneys *In vitro* the substance is active against a wide range of gram negative organisms No induced resistance to the antibiotic was observed The Wellcome group reports that the A compound is superior to the D forms in experimental whooping cough infections and in acute infections with *Eberthela typhosus* At John Hopkins Medical School the doses used was either 3 mgm/kg body weight intramuscularly per day in 8 doses or 7 mgm/kg per day in 3 doses The latter was not tolerated f for more than 2 to 3 days Treatment was usually continued for 5 to 10 days Of the 22 patients treated, the clinical results are described as good or excellent in those with infections due to *Pseudomonas aeruginosa H pertusis Aer bacter a rogenes, K pneumonia, E coli* and in Brucellosis In pertusis the results are particularly striking with small infants who are seriously ill Good results are also quoted in infantile gastro enteritis when the drug is given orally In severe instances of such infections the total daily dose of polymyxin has been based upon 3 to 5 mgms of the antibiotic per kg of body weight this being split into 8 equal doses and given in a special buffer solution (pH 7 4) at interval of 3 hours

Polymyxin is moderately toxic for white mice the LD_{50} being 250 to 300 milligram per kilogram when given by a single subcutaneous injection In large animals such as dogs 10 milligram of polymyxin D per kilogram given twice day for 7 days by the intramuscular route was well tolerated All samples o polymyxin tested have produced albumin, casts, white and red blood cells in th urine of rats which had received 20 mgm per kgm of polymyxin daily by t intravenous route

Polymyxin passes readily into the blood stream following its intramuscu injection into dogs When polymyxin was administered to human beings devided doses by the intramuscular route at intervals of 3 hours in amounts to exceed a total daily dose of 3 mgm per kgm of body weight, concentrat of 0 6 to 1 3 micrograms of the antibiotic per c c were noted in the serum a 24 hours of therapy Detectable amounts of the antibiotic were present in

All specimens of this antibiotic which has been tested have produced varying degrees of renal tubular dysfunction In the mildest form it appears as *fixation of the specific gravity* of the urine, while in severe forms, oliguria with albumin casts red blood cells and white cells in the urine, an elevated non protein nitrogen and depressed renal function *may occur These latter reaction* sometime become very disturbing and it is because of them that the general use of polymyxin seems contra indicated Histamine like reactions, hyperesthesias and fever have been noted in the course of polymyxin therapy, but these reactions would appear to be due to impurities in the specimens of polymyxin which were being used, rather than to the *antibiotic itself*

6. Tyrothricin (Gramicidin & Tyrocidine)

When bacillus brevis is grown in one per cent tryptone broth for four days at 37°C it produces a substance which was first called gramicidin Thus substance along with tyrocidine was later known as tyrothricin which has bactericidal properties against most gram positive coccal pathogens with the possible exceptions of strains of *Staph aureus* It also under certain conditions acts on certain gram negative species Tyrothricin is effective in the treatment of experimental infections with hæmolytic streptococcus Both gramicidine and tyrocidine hydrochloride are crystalline substances which are stable in alcohol even at high temperature they are feebly soluble in water, but fairly stable in colloidal emulsions *Str fæcalis* and related fæcal streptococci are sensitive to the action of tyrothricin, it therefore exercises a selective action In animal experiments tyrothricin and its components are only effective when placed in direct contact with the infecting *bacteria and not when they are given by the mouth* or systemically when the infection is given intraperitoneally

Toxicity—It has been *shown that both fractions of tyrothricin produce hæmolysis* when given by the intravenous route and this action precludes their successful use against organisms circulating in the blood Efforts to get rid of hæmolytic effect have not been *successful so far Daily intravenous injections of 20 mgm* of gramicidin or tyrothricin per kg body weight produced death within 2 to 8 days the animals losing appetite for food loss in weight and the red blood cells fell from 6 million to 2½ million per ccm All these substances are definitely toxic on intraperitoneal and intravenous injections but not when given by mouth They are therefore destroyed in the gastro intestinal tract or are not absorbed

Tyrothricin and tyrocidine in high concentrations produce cytoplasmic and nuclear disintegration of polymorphonuclear leucocytes though no apparent injury occurred to the cells and they continued to phagocytose bacteria Gramicidin is more toxic in this respect than tyrocidine and the cytotoxicity of tyrothricin is largely due to its gramicidine content Acute toxicity of tyrothricin and its fractions has been observed in rabbits and dogs death resulting within a few days when it is given intravenously Tyrothricin and its two fractions have no marked antibacterial properties and when used locally (in alcoholic or aqueous solution) do not produce serious toxic effects

Of the three substances tyrothricin is the most suitable for local use as it is fairly *easily prepared and easily* obtainable There is some selective difference between the action of gramicidin and tyrocidine the latter being slightly active against gram negative *organisms*

The most satisfactory responses were in cases in which ulcers are infected with *Str pyogenes*, in the treatment of infections with *Staph aureus* the results were less satisfactory Tyrothricin is also of definite value in the treatment of certain types of infected ulcers of ischæmic and stasis origin For small ulcers a sterile cotton pad is saturated with the aqueous solution with a dropper every hour the pad was changed every 24 hours or after if there was much discharge Tyrothricin is useful in preparation for skin grafting of infected ulcers and wounds with *Str pyogenes* and *Staph aureus* the infecting organisms are thus eliminated

7. Gramicidin S

Gramicidin S is produced from *B brevis var gause brasilinkoza* Improvements have been made during recent years on large scale production of gramicidin S (from rough tryptone) in U S S R and the yield is now ... nutritive medium A study of its *chemistry* ... consisting of five different amino acid residues)

and
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baci
organisms is reduced in the presence of blood It kills enterococci which play an important part in septic processes and which are resistant to penicillin and sulphonamides Experiments have shown that epithelisation of wourds treated with gramicidin S is more rapid Its application to wounds prevents suppuration effectively It is now being used in surface wound dressing

8. Streptothricin

The substance was first discovered in 1942 and in addition to its antibacterial activity against certain gram positive pathogenic bacteria it is also active against certain gram negative organisms Streptothricin has been isolated from soil organism of the genus Actinomyces identified as *Actinomyces lavendulae* It is produced when the organism is grown in a tap water medium containing 1 per cent glucose or starch 0 5 per cent tryptone 0.2 per cent potassium phosphate 0 2 per cent sodium chloride 0 001 per cent ferrous sulphate and 0 25 per cent agar This substance is readily soluble in water dilute mineral acids but is destroyed by concentrated acids It is insoluble in ether petroleum ether or chloroform From the tryptone medium it is precipitated by substances which precipitate proteins but it has not the characteristics of proteins On electro dialysis the active substances is found to move to the cathode at a pH of 7 and behaves as an organic base Streptothricin is produced much more readily and abundantly under conditions of submersion combined with agitation and aeration

Activity of Streptothricin in Vitro and in Vivo—Streptothricin possesses bactericidal properties especially against certain gram negative bacteria *e g E coli* It offers some promise as an bactericidal agent against brucellosis in animals 0 1 mgm of crude streptothricin per 10 ccm of broth preventing growth of this organism In guinea pigs infected with *Brucella abortus* 600 mgm of crude streptothricin sterilized the blood Streptothricin inhibited completely the activity of the group of Eberthella typhi The genus clostridium (tetani, welchii septique and sordeli) and certain other organisms such as *B pyocyanous B proteus, Str viridans* and *Str lactis* were also resistant to its action

Streptothricin is suitable for application to infected wounds and mucous membranes and 0 5 to 1 0 per cent solution in normal saline does not injure the conjunctiva This substance should prove useful in the local treatment of infected wounds and burns Unlike other antibiotic agents, streptothricin can be given orally and markedly decreases the number of lactose fermenting bacteria in the intestinal canal It is therefore believed that it may be of value in the treatment of certain types of dysentery and other infections caused by susceptible bacteria (para-typhoid organisms, etc) It is however not advisable to give it by the intravenous or subcutaneous routes in the treatment of systemic infections

As in the case of penicillin, the unit of streptothricin is the amount by weight of streptothricin which will completely inhibit the growth of the test organism (bacillus subtilis in this case) The unit of streptothricin is the minimum quantity of the drug which when added to one ccm of nutrient broth will inhibit growth of inoculum of *E coli*

Streptothricin given subcutaneously or intravenously to experimental animals may at times produce either early or delayed death It is not, therefore, suitable for systemic use

Prep *Acti gram path* *Loc use* *Esti pote* *Pos clini*

9. Circulin

As recently announced by Murray and Tetrault (1948), it is an antibiotic which is more active against gram negative than gram positive bacteria and has been obtained from a strain of bacteria closely resembling *Bacillus circulans* It is very soluble in water, soluble in alcohol but insoluble in the hydrocarbons The antibiotic retains its activity when stored at a pH of 2 5 to 6.5 at 4°C for at least 3 months and is also stable to autoclaving for 15 minutes at 15 pounds pressure in the same pH range This antibiotic has a bacterial activity similar to polymyxin and aerosporin but it is less active than polymyxin ag[illegible] than polymyxin against gram positive bacte[illegible] Circulin appeares to l[illegible] xin. It is active in viv[illegible]

10. Subtilin

Subtilin, an antibiotic agent discovered by Jansen and Hirschmann (1944) Salle and Jann (1945) reported that subtilin in dilution of 1 50,000 prevented surface growth of *Mycobacterium tuberculosis* on Long's synthetic medium They concluded that 'subtilin is bacteriostatic in high dilution and germicidal in greater concentrations'.

Subtilin had a moderate inhibitory effect on the growth of the H37 Rv strain of the tubercle bacillus in sorbitan monooleate albumin liquid medium, but very little effect in the other three media that did not contain sorbitan monooleate Subtilin did not influence the course of a tuberculous infection in guinea pig produced by the H37 Rv strain of tubercle bacillus

11. Bacitracin

Bacitracin, an antibiotic produced by strains of *bacillus subtilis*, was used in 105 cases of surgical infection, refractory to sulpha drugs or other antibiotics There was favourable response in 70 per cent of the cases and in 1/5th of these the results were spectacular Three cases of extensive progressive gangrene responded within 72 hours and recoverd with surgical excision Most of the cases of cellulitis, deep abscess and infected accidental wound made a favourable response A considerable number of staphylococcal strains are noticed resistant to penicillin but susceptable to bacitracin The cases that exhibited

12. Biocerin

was reported to exhibit marked antagonism
nisms, e g salmonella and shigella. The
re produced by an organism isolated from
the identification of ærobic sporeforming

Biocerin was produced by growing *Bacillus cereus* in a medium containing glucose 20 g, $NH_4H_2PO_4$ 1 0 g Methionine 0 005 g, Agar 5 0 g, distilled water 1,000 ml final pH=7 0. All bacterial species tested are inhibited by a concentration of 1 0 mg of crude biocerin per ml of agar

Salmonella paratyphosus A, Salmonella paratyphosus B, Staphylococcus aureus and *Staphyllococcus albus* were not inhibited by a concentration of a 0 5 mgm of crude biocerin per ml of agar

The toxicity of crude biocerin was determined by suspending the material in sterile mineral oil and inject intraperitoneally into white mice weighing approximately 18 20 gms A single injection of 20 mgm of crude substance produced no fatalities in a group of 10 mice at the end of a 5 day test period

13. Miscellaneous Antibiotics

Pyocyanase is a thermostable substance of lipoid nature. Pyocyanine is a blue pigment soluble in chloroform Although these substances were active against certain gram positive and gram negative pathogens, they were found to be very toxic in experimental animals, intra peritoneal injection of 2 mgm of pyocyanine produced death in the animal

Actinomycin A is produced by Actinomyces antibioticus and is an orange coloured highly toxic substance soluble in ether or alcohol Actinomycin B is soluble in ether and insoluble in alcohol Both are exceedingly toxic

Actinomycin A is produced by *Actinomyces antibioticus* and is an orange coloured substance readily soluble in water It is active against gram positive bacteria and colon typhoid salmonella group of gram negative organism Little is known about its therapeutic value

Citrinin is produced by *penicillium citrium* and is a yellow substance which is toxic to animals when given by the mouth or intraperitoneally.

Gliotoxin is produced by *Trichoderma lignorum* It is active against certain gram positive organisms and also against gram negative pathogens It is toxic and holds little promise as a chemotherapeutic agent *Glioto*

Fumigatin is derived from *Aspergillus fumigatus* is soluble and is very active against certain gram positive organisms *Fumig*

Claviformin is obtained from cultures of Penicillium claviforme clavacin from *Aspergillus clavatus* and patulin from *Penicillium patulum* They all have the same empirical formula Patulin has been tried with beneficial results in the treatment of common colds 1 in 10 000 solutions being sprayed into the nose or snuffed up from the hand. None of these substances are suitable for subcutaneous or intravenous administration on account of their high degree of toxicity *Clavif Clava Patul*

Fumigacin and helvolic acid are produced by *Aspergillus fumigatus* In pure form fumigacin occurs as fine white needles Both these substances are toxic to experimental animals *Fumi helvol*

Aspergillic acid was obtained from *Aspergillus flavus* and occurs in crystalline form It is too toxic for systemic use but it may be useful for local application in gas gangrene *Asper*

Flavicin was also isolated from *Aspergillus flavus* It is soluble in water and ether and has low toxicity and high antibacterial activity in the same way as penicillin There is therefore, possibility of another therapeutic agent comparable with penicillin *Flavic*

Gigantic acid is obtained from *Aspergillus giganteus* It closely resembles penicillin in its properties *Gigna*

Flavicidin and penicillin protect mice to an equal degree against pneumococcal infection *It is highly soluble* and readily absorbed by the body tissues *it is excreted by the kidneys* The organisms rendered resistant to penicillin were also found to be resistant to flavicidin *Flavi*

Antibiotic substances of non microbial origin

The antibiotic substances described above are derived from micro organisms The following antibiotic agents are derived from other natural sources —

Lysozyme chlorellin canavalin and allicin

Lysozyme was first discovered by Fleming in 1922 in the nasal secretions of a patient suffering from coryza He also showed that nasal mucus possesses a *powerful inhibitory* and lytic action on different organisms and that this action was also possessed by some animal and vegetable tissues and various secretions of the human body Lysozyme occurs in tears sputum saliva, blood serum and plasma peritoneal fluid effusion sebum semen etc but is not found in normal urine cerebrospinal fluid or sweat It is stable and maintains its activity in fluids for many weeks the dry material also does not deteriorate Lysozyme occurs in large quantities in commercial dried egg albumin prepared weeks and months ago It is soluble in water insoluble in alcohol ether chloroform acetone xylol etc The substance appears to be of a protein nature of low molecular weight It has the power of splitting carbohydrates and belongs to the class of carbohydrates It is not of any marked significance as a chemotherapeutic agent *Lyso*

Chlorellin was obtained from unicellular algae *Chlorella vulgaris* and *Chlorella pyrenoidosa* when cultured in solution of mineral nutrients used for algal cultures This substance inhibits growth of staphylococci and of *Str pyogenes* as well as growth of gram negative *E coli* The presence of rabbit's serum does not interfere with its antibacterial activity Further studies are being carried out with regard to its therapeutic and toxic properties *Chl*

Canavalin is obtained from soyabean or jack bean flour in a mixture of water and organic solvents such ... effective against *Staph aureus* and inhibit the gro... It has been tried in the *treatment of* ... erage dose per day being 30 ccm given ... progress

Allicin is the antibacterial principle occuring in *Allium sativum* (the common garlic) The compound is said to contain about 40 per cent of sulphur no nitrogen and no halogens *Allic*

effective against gram positive and gram negative organisms Its effectiveness against *Staph aureus* is equal to approximately 15 units of penicillin per mgm and its activity is not affected by the presence of para aminobenzoic acid In dilutions of 1 in 125000 this substance inhibits the growth of large number of gram positive and gram negative organisms including *Staph aureus, Str viridans, Bacillus subtilis, Eberthella typhi* and other members of colon typhoid dysentery group It remains to be seen whether it will be of any chemo therapeutic value or not

A number of other antibacterial agents or antibiotic substances occur in nature and certain flowering plants and weeds are found to contain them There is a very large field waiting for the investigation of these

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P

PAGE

ERRATA

Page	Para	Line	Corrections
3	4	4	For '6×10' read '6×10^{23}'
21	5	5	For 'atomiseris' read 'atomiser is'
48	4	2	For 'grain' read gram'
49	2	4	After 'increase read 'this
66	last	2	For 'distention read 'tension'
74	5	13	After 'pressure read 'are present'
91	2	7	After taken read for its'
91	4	2	For 'sandards read standards'
129	1	3	For 'hydroscopic read hydropic'
152	1	2	For lessions read 'lesions
206	3	2	After female read is
256	1	1	For 'non read uni
256	under classification of protozoal		The names of species are misplaced—no[...] the proper genus read opposite respec[...]
256	under classification of protozoal—No II		For mans read means
270	side heading		With differential read diagnosis
276	7	7	For powders read pills
293	last	6	After tablets read (Full stop)
303	7	3	For vala read ovata'
304	side heading		For clinical read chemical
316	3	16	For 'gm read 'mgm
332	4	3	For Sb iv read Sb iii
337	last para	last line	for 0·25 read 0·075
341	1	16	For different read difficult
346	last para	last line	After route read large'
350	1	3	For 'gm read out
350	1	5	For gm read mgm
352	1	1	After potassium read iodide'
353	3	1	For amomatic' read aromatic
358	1	4	For which read schizogony'
371	2	3	For Racial read Radical
377	under species of cinchona		For crown read 'Trown
418	2	7	Omit count after 'hemoglobin
42[illegible]	5	5	For % read 3
432	1	16	For calls read cells
436	6		For rate read rats
437	1	7	For rage read range
438	1	1	For sanctochin read santochin
471	2	-	For round read found
483	1	1	For 30,000 read 100,000
501	last	1	For 0·01 read 0·1
517	-	3	For 20 read 2·0
519	2	1	After this read ,
535	2	-	For lucocyte read leucocytes
557	2	2	For Diseases read cases
562	5	last	After 1 read KK
594	4	18	For '300 read 3·00
614	last	1	For Phthaly read Phthalyl
620	3	7	For "enables the maintenance of adequate concentration in the affected read "and epileptiform symptoms may be prod[...] Sulphaguanidine is"